

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-492**

**Final Printed Labeling**

1 version 8-6-02  
2 revised 8-9-02

3  
4 **ELOXATIN™**  
5 **(oxaliplatin for injection)**  
6

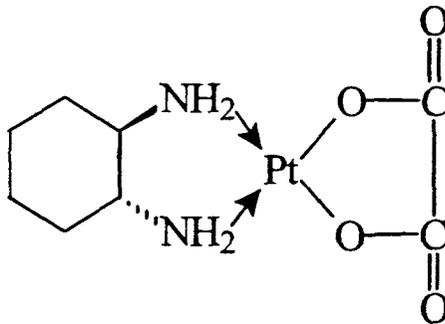
7  
8 **WARNING**

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

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

9  
10 **DESCRIPTION**

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



15  
16  
17 The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very  
18 slightly soluble in methanol, and practically insoluble in ethanol and acetone.

19  
20 ELOXATIN is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile,  
21 preservative-free lyophilized powder for reconstitution. Lactose monohydrate is present as an  
22 inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths,  
23 respectively.

24

25

## 26 CLINICAL PHARMACOLOGY

27

### 28 Mechanism of Action

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

36

### 37 Pharmacology

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

42

### 43 Human Pharmacokinetics

44 The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma  
45 ultrafiltrate. The decline of ultrafilterable platinum levels following oxaliplatin administration  
46 is triphasic, characterized by two relatively short distribution phases ( $t_{1/2\alpha}$ ; 0.43 hours and  $t_{1/2\beta}$ ;  
47 16.8 hours) and a long terminal elimination phase ( $t_{1/2\gamma}$ ; 391 hours). Pharmacokinetic parameters  
48 obtained after a single 2-hour IV infusion of ELOXATIN at a dose of 85 mg/m<sup>2</sup> expressed as  
49 ultrafilterable platinum were  $C_{\max}$  of 0.814 µg/mL and volume of distribution of 440 L.

50

51 Interpatient and inpatient variability in ultrafilterable platinum exposure ( $AUC_{0-48}$ ) assessed  
52 over 3 cycles was moderate to low (23% and 6%, respectively). A pharmacodynamic  
53 relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not  
54 been established.

55

### 56 Distribution

57 At the end of a 2-hour infusion of ELOXATIN, approximately 15% of the administered  
58 platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into  
59 tissues or eliminated in the urine. In patients, plasma protein binding of platinum is irreversible  
60 and is greater than 90%. The main binding proteins are albumin and gamma-globulins.  
61 Platinum also binds irreversibly and accumulates (approximately 2-fold) in erythrocytes, where  
62 it appears to have no relevant activity. No platinum accumulation was observed in plasma  
63 ultrafiltrate following 85 mg/m<sup>2</sup> every two weeks.

64

65

## 66 **Metabolism**

67 Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation. There is no  
68 evidence of cytochrome P450-mediated metabolism *in vitro*.

69

70 Up to 17 platinum-containing derivatives have been observed in plasma ultrafiltrate samples  
71 from patients, including several cytotoxic species (monochloro DACH platinum, dichloro  
72 DACH platinum, and monoquo and diaquo DACH platinum) and a number of noncytotoxic,  
73 conjugated species.

74

## 75 **Elimination**

76 The major route of platinum elimination is renal excretion. At five days after a single 2-hour  
77 infusion of ELOXATIN, urinary elimination accounted for about 54% of the platinum  
78 eliminated, with fecal excretion accounting for only about 2%. Platinum was cleared from  
79 plasma at a rate (10 – 17 L/h) that was similar to or exceeded the average human glomerular  
80 filtration rate (GFR; 7.5 L/h). There was no significant effect of gender on the clearance of  
81 ultrafilterable platinum. The renal clearance of ultrafilterable platinum is significantly  
82 correlated with GFR. (See ADVERSE REACTIONS)

83

## 84 **Pharmacokinetics in Special Populations**

### 85 **Renal Impairment**

86

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

92

### 93 **Drug - Drug Interactions**

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

101

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

105

106 **CLINICAL STUDIES**

107

108 **Combination Therapy with ELOXATIN and Infusional 5-FU/LV in Previously**  
 109 **Treated Patients with Advanced Colorectal Cancer**

110 A multicenter, randomized, three arm controlled study was conducted in the US and Canada  
 111 comparing the efficacy and safety of ELOXATIN in combination with an infusional schedule of  
 112 5-FU/LV to the same dose and schedule of 5-FU/LV alone and to single agent oxaliplatin in  
 113 patients with advanced colorectal cancer who had relapsed/progressed during or within 6  
 114 months of first line therapy with bolus 5-FU/LV and irinotecan. The study was intended to be  
 115 analyzed for response rate after 450 patients were enrolled. Survival will be subsequently  
 116 assessed in all patients enrolled in the completed study. Accrual to this study is complete, with  
 117 821 patients enrolled. Patients in the study had to be at least 18 years of age, have  
 118 unresectable, measurable, histologically proven colorectal adenocarcinoma, with a Karnofsky  
 119 performance status >50%. Patients had to have SGOT(AST) and SGPT(ALT) ≤ 2x the  
 120 institution's upper limit of normal (ULN), unless liver metastases were present and documented  
 121 at baseline by CT or MRI scan, in which case ≤ 5x ULN was permitted. Patients had to have  
 122 alkaline phosphatase ≤ 2x the institution's ULN, unless liver metastases were present and  
 123 documented at baseline by CT or MRI scan, in which cases ≤ 5x ULN was permitted. Prior  
 124 radiotherapy was permitted if it had been completed at least 3 weeks before randomization.

125

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

127

128 **Table 1 – Dosing Regimens in Refractory and Relapsed**  
 129 **Colorectal Cancer Clinical Trial**

129

130

Treatment Arm	Dose	Regime n
ELOXATIN + 5-FU/LV (N=152)	Day 1: ELOXATIN: 85 mg/m <sup>2</sup> (2-hour infusion) + LV 200 mg/m <sup>2</sup> (2-hour infusion), followed by 5-FU: 400 mg/m <sup>2</sup> (bolus), 600 mg/m <sup>2</sup> (22-hour infusion)  Day 2: LV 200 mg/m <sup>2</sup> (2-hour infusion), followed by 5-FU: 400 mg/m <sup>2</sup> (bolus), 600 mg/m <sup>2</sup> (22-hour infusion)	q2w
5-FU/LV (N=151)	Day 1: LV 200 mg/m <sup>2</sup> (2-hour infusion), followed by 5-FU: 400 mg/m <sup>2</sup> (bolus), 600 mg/m <sup>2</sup> (22-hour infusion)  Day 2: LV 200 mg/m <sup>2</sup> (2-hour infusion), followed by 5-FU: 400 mg/m <sup>2</sup> (bolus), 600 mg/m <sup>2</sup> (22-hour infusion)	q2w
ELOXATIN (N=156)	Day 1: ELOXATIN 85 mg/m <sup>2</sup> (2-hour infusion)	q2w

131

132

133 Patients entered into the study for evaluation of response must have had at least one  
134 unidimensional lesion measuring  $\geq 20$ mm using conventional CT or MRI scans, or  $\geq 10$ mm using  
135 a spiral CT scan. Tumor response and progression were assessed every 3 cycles (6 weeks)  
136 using the Response Evaluation Criteria in Solid Tumors (RECIST) until radiological  
137 documentation of progression or for 13 months following the first dose of study drug(s),  
138 whichever came first. Confirmed responses were based on two tumor assessments separated by  
139 at least 4 weeks.  
140

141  
142  
143  
144  
145  
146

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

**Table 2 – Patient Demographics in Refractory and Relapsed  
Colorectal Cancer Clinical Trial**

	<b>5-FU/LV (N = 151)</b>	<b>ELOXATIN (N = 156)</b>	<b>ELOXATIN + 5-FU/LV (N = 152)</b>
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
<b>Race (%)</b>			
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
<b>KPS (%)</b>			
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
<b>Number of metastatic sites (%)</b>			
1	27.2	31.4	25.7
≥2	72.2	67.9	74.3
<b>Liver involvement (%)</b>			
Liver only	22.5	25.6	18.4
Liver + other	60.3	59.0	53.3

147  
148  
149  
150  
151  
152  
153  
154

The median number of cycles administered per patient was 6 for the ELOXATIN and infusional 5-FU/LV combination and 3 each for infusional 5-FU/LV alone and ELOXATIN alone.

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

155  
156  
157

**Table 3 - Response Rates (ITT Analysis)**

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

158  
159  
160

**Table 4 - Summary of Radiographic Time to Progression\***

Arm	5-FU/LV (N=151)	ELOXATIN (N=156)	ELOXATIN + 5-FU/LV (N=152)
No. of Progressors	74	101	50
No. of patients with no radiological evaluation beyond baseline	22 (15%)	16 (10%)	17 (11%)
Median TTP (months)	2.7	1.6	4.6
95% CI	1.8-3.0	1.4-2.7	4.2-6.1

161  
162  
163  
164  
165

\*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.

166  
167  
168  
169

At the time of the interim analysis 49% of the radiographic progression events had occurred. In this interim analysis an estimated 2-month increase in median time to radiographic progression was observed compared to infusional 5-FU/LV alone.

170  
171  
172  
173

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

174  
175

#### **INDICATIONS AND USAGE**

176  
177  
178  
179  
180  
181

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

182

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

187

## 188 **CONTRAINDICATIONS**

189

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

192

## 193 **WARNINGS**

194

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

202

## 203 **Pregnancy Category D**

204 ELOXATIN may cause fetal harm when administered to a pregnant woman. Pregnant rats were  
205 administered 1 mg/kg/day oxaliplatin (less than one-tenth the recommended human dose based  
206 on body surface area) during gestation days 1-5 (pre-implantation), 6-10, or 11-16 (during  
207 organogenesis). Oxaliplatin caused developmental mortality (increased early resorptions) when  
208 administered on days 6-10 and 11-16 and adversely affected fetal growth (decreased fetal  
209 weight, delayed ossification) when administered on days 6-10. If this drug is used during  
210 pregnancy or if the patient becomes pregnant while taking this drug, the patient should be  
211 apprised of the potential hazard to the fetus. Women of childbearing potential should be advised  
212 to avoid becoming pregnant while receiving treatment with ELOXATIN.

213

## 214 **PRECAUTIONS**

215

### 216 **General**

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

221

222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261

**Neuropathy:**

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

ELOXATIN is associated with two types of neuropathy:

- **An acute, reversible primarily peripheral sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing.** The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received ELOXATIN with infusional 5-FU/LV. In any individual cycle acute neurotoxicity was observed in approximately 30% of patients. Ice (mucositis prophylaxis) should be avoided during the infusion of ELOXATIN because cold temperature can exacerbate acute neurological symptoms. (See DOSAGE AND ADMINISTRATION: Dose Modifications).

An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% of patients is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing).

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

Neurotoxicity scale:

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

262

263 **Pulmonary Toxicity**

264

265 ELOXATIN has been associated with pulmonary fibrosis (0.7% of study patients), which may  
266 be fatal. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea,  
267 crackles, or radiological pulmonary infiltrates, ELOXATIN should be discontinued until further  
268 pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

269

270

271 **Information for Patients**

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

278

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

282

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

285

286 **Laboratory Tests**

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

290

291 **Laboratory Test Interactions**

292 None known.

293

294 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

300

301 In a fertility study, male rats were given oxaliplatin at 0, 0.5, 1, or 2 mg/kg/day for five days  
302 every 21 days for a total of three cycles prior to mating with females that received two cycles  
303 of oxaliplatin on the same schedule. A dose of 2 mg/kg/day (less than one-seventh the  
304 recommended human dose on a body surface area basis) did not affect pregnancy rate, but

305

306  
307 caused developmental mortality (increased early resorptions, decreased live fetuses, decreased  
308 live births) and delayed growth (decreased fetal weight). Testicular damage, characterized by  
309 degeneration, hypoplasia, and atrophy, was observed in dogs administered oxaliplatin at 0.75  
310 mg/kg/day x 5 days every 28 days for three cycles. A no effect level was not identified. This  
311 daily dose is approximately one-sixth of the recommended human dose on a body surface area  
312 basis.

313  
314 **Pregnancy Category D - See WARNINGS**

315 **Nursing Mothers** - It is not known whether ELOXATIN or its derivatives are excreted in  
316 human milk. Because many drugs are excreted in human milk and because of the potential for  
317 serious adverse reactions in nursing infants from ELOXATIN, a decision should be made  
318 whether to discontinue nursing or delay the use of the drug, taking into account the importance  
319 of the drug to the mother.

320  
321 **Pediatric Use** - The safety and effectiveness of ELOXATIN in pediatric patients have not been  
322 established.

323  
324 **Patients with Renal Impairment** - The safety and effectiveness of the combination of  
325 ELOXATIN and infusional 5-FU/LV in patients with renal impairment has not been evaluated.  
326 The combination of ELOXATIN and infusional 5-FU/LV should be used with caution in  
327 patients with preexisting renal impairment since the primary route of platinum elimination is  
328 renal. Clearance of ultrafilterable platinum is decreased in patients with mild, moderate, and  
329 severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate  
330 levels and clinical safety and effectiveness has not been established. (see CLINICAL  
331 PHARMACOLOGY and ADVERSE REACTIONS)

332  
333 **Geriatric Use** - No significant effect of age on the clearance of ultrafilterable platinum has  
334 been observed. In the randomized clinical trial (see CLINICAL STUDIES) of ELOXATIN, 95  
335 patients treated with ELOXATIN and infusional 5-FU/LV were <65 years and 55 patients were ≥  
336 65 years. The rates of overall adverse events, including grade 3 and 4 events, were similar  
337 across and within arms in the different age groups. The incidence of diarrhea, dehydration,  
338 hypokalemia, and fatigue were higher in patients ≥65 years old.

339  
340 **Drug Interactions** - No specific cytochrome P-450-based drug interaction studies have been  
341 conducted. No pharmacokinetic interaction between 85 mg/m<sup>2</sup> ELOXATIN and infusional 5-FU  
342 has been observed in patients treated every 2 weeks. Increases of 5-FU plasma concentrations  
343 by approximately 20% have been observed with doses of 130 mg/m<sup>2</sup> ELOXATIN dosed every  
344 3 weeks. Since platinum containing species are eliminated primarily through the kidney,  
345 clearance of these products may be decreased by coadministration of potentially nephrotoxic  
346 compounds; although, this has not been specifically studied. (see CLINICAL  
347 PHARMACOLOGY)

348

349 **ADVERSE REACTIONS**

350

351 More than 1500 patients with advanced colorectal cancer have been treated in clinical studies  
352 with Eloxatin either as a single agent or in combination with other medications. The most  
353 common adverse reactions were peripheral sensory neuropathies, neutropenia, nausea, emesis,  
354 and diarrhea (See PRECAUTIONS). Four-hundred and fifty patients (about 150 receiving the  
355 combination of ELOXATIN and 5-FU/LV) were studied in a randomized trial in patients with  
356 refractory and relapsed colorectal cancer (See CLINICAL STUDIES). The adverse event  
357 profile in this study was similar to that seen in other studies and the adverse reactions in this  
358 trial are shown in the tables below.

359

360 Thirteen per cent of patients in the ELOXATIN and infusional 5-FU/LV-combination arm and  
361 18% in the infusional 5-FU/LV arm had to discontinue treatment because of adverse effects  
362 related to gastrointestinal or hematologic adverse events, or neuropathies. Both 5-FU and  
363 ELOXATIN are associated with gastrointestinal and hematologic adverse events. When  
364 ELOXATIN is administered in combination with infusional 5-FU, the incidence of these events  
365 is increased.

366

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

372

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

378  
379  
380  
381

**Table 5 – Adverse Experience Reported In Colorectal Cancer Clinical Trial**  
(≥5% of all patients and with ≥1% NCI Grade 3/4 events)

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

382  
383  
384  
385  
386

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

387  
388  
389  
390

**Table 6 - Adverse Experience Reported In Colorectal Cancer Clinical Trial**  
(≥5% of all patients but with <1% NCI Grade 3/4 events)

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

391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401

Adverse events were similar in men and women and in patients <65 and ≥65 years, but older patients may have been more susceptible to dehydration, diarrhea, hypokalemia and fatigue. The following additional adverse events, at least possibly related to treatment and potentially important, were reported in ≥2% and <5% of the patients in the ELOXATIN and infusional 5-FU/LV combination arm (listed in decreasing order of frequency): anxiety, myalgia, erythematous rash, increased sweating, conjunctivitis, weight decrease, dry mouth, rectal hemorrhage, depression, ataxia, ascites, hemorrhoids, muscle weakness, nervousness, tachycardia, abnormal micturition frequency, dry skin, pruritis, hemoptysis, purpura, vaginal hemorrhage, melena, somnolence, pneumonia, proctitis, involuntary muscle contractions, intestinal obstruction, gingivitis, tenesmus, hot flashes, enlarged abdomen, urinary incontinence.

402

403 **Hematologic**

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

406

407

**Table 7 – Adverse Hematologic Experiences  
(≥5% of patients)**

408

409

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

410

411 **Thrombocytopenia**

412 Thrombocytopenia was frequently reported with the combination of ELOXATIN and infusional  
413 5-FU/LV. The incidence of Grade 3/4 thrombocytopenia was 4%. Grade 3/4 hemorrhagic  
414 events were reported at low frequency and the incidence of these events was similar for the  
415 combination of ELOXATIN and infusional 5-FU/LV and the infusional 5-FU/LV control group.  
416 The incidence of all hemorrhagic events, however, was higher on the ELOXATIN combination  
417 arm compared to the 5-FU/LV arm. These events included gastrointestinal bleeding, hematuria  
418 and epistaxis.

419

420 **Neutropenia**

421 Neutropenia was frequently observed with the combination of ELOXATIN and infusional  
422 5-FU/LV, with Grade 3 and 4 events reported in 27% and 17% of previously treated patients,  
423 respectively. The incidence of febrile neutropenia was 1% in the infusional 5-FU/LV arm and  
424 6% (less than 1% of cycles) in the ELOXATIN and infusional 5-FU/LV combination arm.

425

426 **Gastrointestinal**

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

430

431 The incidence of gastrointestinal adverse events appears to be similar across cycles.  
432 Premedication with antiemetics, including 5-HT<sub>3</sub> blockers, is recommended. Diarrhea and  
433 mucositis may be exacerbated by the addition of ELOXATIN to infusional 5-FU/LV, and should  
434 be managed with appropriate supportive care. Since cold temperature can exacerbate acute  
435 neurological symptoms, ice (mucositis prophylaxis) should be avoided during the infusion of  
436 ELOXATIN.

437

438 **Dermatologic**

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

442

443 **Care of Intravenous Site:**

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

447

448 **Neurologic**

449 ELOXATIN is consistently associated with two types of peripheral neuropathy (see  
450 PRECAUTIONS, Neuropathy). Seventy-four percent of patients experienced neuropathy.  
451 The incidence of overall and Grade 3/4 persistent peripheral neuropathy was 48% and 6%,  
452 respectively, in the study. These events can occur without any prior acute event. The majority  
453 of the patients (80%) that developed grade 3 persistent neuropathy progressed from prior Grade  
454 1 or 2 events. The median number of cycles administered on the ELOXATIN with infusional 5-  
455 FU/LV combination arm was 6 cycles. In clinical trials that have studied similar administration  
456 schedules of this combination regimen, (median cycles ranged 10-12), a higher incidence  
457 (17%) of Grade 3/4 persistent neurotoxicity was observed.

458

459 **Allergic reactions**

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

466

467 **Renal**

468 About 10% of patients in all groups had some degree of elevation of serum creatinine. The  
469 incidence of Grade 3/4 elevations in serum creatinine in the ELOXATIN and infusional  
470 5-FU/LV combination arm was 1%.

471

472 **Hepatic**

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

475  
476  
477  
478

**Table 8. – Adverse Hepatic – Clinical Chemistry Experience  
(≥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	26	1	31	0
AST (SGOT-ASAT)	39	2	54	4	47	0
Total Bilirubin	22	6	13	5	13	1

479  
480

### **Thromboembolism**

482

483 The incidence of thromboembolic events was 4% in the infusional 5-FU/LV arm, and 9% in the  
484 ELOXATIN and infusional 5-FU/LV combination arm.

485

486

### **Postmarketing Experience**

488

489 The following events have been reported from worldwide postmarketing experience.

490

#### Body as a whole:

492 - angioedema, anaphylactic shock

493

#### Central and peripheral nervous system disorders:

495 - loss of deep tendon reflexes, dysarthria, Lhermittes' sign, cranial nerve palsies,  
496 fasciculations

497

#### Gastrointestinal system disorders:

499 - severe diarrhea/vomiting resulting in hypokalemia, metabolic acidosis; ileus; intestinal  
500 obstruction, pancreatitis

501

#### Hearing and vestibular system disorders:

503 - deafness

504

505

#### Platelet, bleeding, and clotting disorders:

507 - immuno-allergic thrombocytopenia

508

#### Red Blood Cell disorders

510 - hemolytic uremic syndrome

511

512

513

514

515 Respiratory system disorders:

516 - pulmonary fibrosis, and other interstitial lung diseases

517

518 Vision disorders:

519 - decrease of visual acuity, visual field disturbance, optic neuritis

520

## 521 **OVERDOSAGE**

522 There have been four ELOXATIN overdoses reported. One patient received two 130 mg/m<sup>2</sup>  
523 doses of ELOXATIN (cumulative dose of 260 mg/m<sup>2</sup>) within a 24 hour period. The patient  
524 experienced Grade 4 thrombocytopenia (<25,000/mm<sup>3</sup>) without any bleeding, which resolved.  
525 Two other patients were mistakenly administered ELOXATIN instead of carboplatin. One  
526 patient received a total ELOXATIN dose of 500 mg and the other received 650 mg. The first  
527 patient experienced dyspnea, wheezing, paresthesia, profuse vomiting and chest pain on the day  
528 of administration. She developed respiratory failure and severe bradycardia, and subsequently  
529 did not respond to resuscitation efforts. The other patient also experienced dyspnea, wheezing,  
530 paresthesia, and vomiting. Her symptoms resolved with supportive care. Another patient who  
531 was mistakenly administered a 700 mg dose experienced rapid onset of dysesthesia. Inpatient  
532 supportive care was given, including hydration, electrolyte support, and platelet transfusion.  
533 Recovery occurred 15 days after the overdose. There is no known antidote for ELOXATIN  
534 overdose. In addition to thrombocytopenia, the anticipated complications of an ELOXATIN  
535 overdose include myelosuppression, nausea and vomiting, diarrhea, and neurotoxicity. Patients  
536 suspected of receiving an overdose should be monitored, and supportive treatment should be  
537 administered.

538

## 539 **DOSAGE AND ADMINISTRATION**

540

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

542

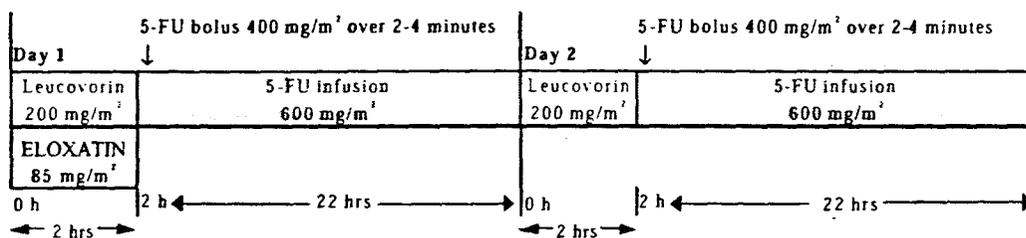
543 Day 1: ELOXATIN 85 mg/m<sup>2</sup> IV infusion in 250-500 mL D5W and leucovorin  
544 200 mg/m<sup>2</sup> IV infusion in D5W both given over 120 minutes at the same time  
545 in separate bags using a Y-line, followed by 5-FU 400 mg/m<sup>2</sup> IV bolus  
546 given over 2-4 minutes, followed by 5-FU 600 mg/m<sup>2</sup> IV infusion in 500 mL  
547 D5W (recommended) as a 22-hour continuous infusion.

548

549 Day 2: Leucovorin 200 mg/m<sup>2</sup> IV infusion over 120 minutes, followed by 5-FU 400  
550 mg/m<sup>2</sup> IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m<sup>2</sup> IV  
551 infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion.

552

553



554 Repeat cycle every 2 weeks.

555

556 The administration of ELOXATIN does not require prehydration.

557

558 Premedication with antiemetics, including 5-HT<sub>3</sub> blockers with or without dexamethasone, is  
 559 recommended.

560

561 For information on 5-fluorouracil and leucovorin, see the respective package inserts.

562

### 563 Dose Modification Recommendations

564 Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and  
 565 laboratory tests (see Laboratory Tests). Neuropathy was graded using a study-specific  
 566 neurotoxicity scale (see PRECAUTIONS, Neuropathy). Other toxicities were graded by the  
 567 NCI CTC, Version 2.0.

568

569 Prolongation of infusion time for ELOXATIN from 2 hours to 6 hours decreases the C<sub>max</sub> by an  
 570 estimated 32% and may mitigate acute toxicities. The infusion time for infusional 5-FU and  
 571 leucovorin do not need to be changed.

572

573 For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose  
 574 reduction of ELOXATIN to 65 mg/m<sup>2</sup> should be considered. For patients with persistent Grade  
 575 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-FU/LV  
 576 regimen need not be altered.

577

578 A dose reduction of ELOXATIN to 65 mg/m<sup>2</sup> and infusional 5-FU by 20% (300 mg/m<sup>2</sup> bolus  
 579 and 500 mg/m<sup>2</sup> 22 hour infusion) is recommended for patients after recovery from grade 3/4  
 580 gastrointestinal (despite prophylactic treatment) or grade 3/4 hematologic toxicity (neutrophils  
 581 <1.5 x 10<sup>9</sup>/L, platelets <100 x 10<sup>9</sup>/L).

582

### 583 Preparation of Infusion Solution

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

587

588

589 The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the  
590 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. **Do not administer**  
591 **the reconstituted solution without further dilution.** The reconstituted solution must be further  
592 diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

593

594 After reconstitution in the original vial, the solution may be stored up to 24 hours under  
595 refrigeration [2-8°C (36-46° F)]. After final dilution with 250-500 mL of  
596 5% Dextrose Injection, USP, the shelf life is **6 hours at room temperature [20-25°C (68-**  
597 **77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].** ELOXATIN is not light  
598 sensitive.

599

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

604

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

607

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

611

## 612 **HOW SUPPLIED**

613

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

618

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

621

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

624

## 625 **Storage**

626 Store under normal lighting conditions at 25°C (77°F); excursions permitted to 15-30°C  
627 (59-86°F) [see USP controlled room temperature].

628

629

630 **Handling and Disposal**

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

636

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

640

641 **REFERENCES**

642

- 643 1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and  
644 Recommendations for Practice. Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.
- 645 2. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH Publication  
646 No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing  
647 Office, Washington, D.C. 20402.
- 648 3. AMA Council Report. Guidelines for handling parenteral antineoplastics. *JAMA*  
649 1985;253(11):1590-1592.
- 650 4. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic  
651 agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on  
652 Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179  
653 Longwood Avenue, Boston, MA 02115.
- 654 5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe  
655 handling of antineoplastic agents. *Med J Australia* 1983;1:426-428.
- 656 6. Jones RB, et al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai  
657 Medical Center. *Ca - A Cancer Journal for Clinicians*. Sept./Oct. 1983:258-263.
- 658 7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on  
659 handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990;47:1033-1049.
- 660 8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice  
661 Guidelines). *Am J Hosp Pharm* 1996;53:1669-1685.

662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674

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

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

Printed in USA  
Date of Revision



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

47

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

51

## 52 **How is ELOXATIN given to me?**

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

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

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

62

### 63 **Treatment Day 1:**

64

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

68

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

72

### 73 **Treatment Day 2:**

74

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

77

## 78 **During your treatment with ELOXATIN:**

79

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

85

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

90

91

92 **What activities should I avoid while under treatment with ELOTAXIN?**

93

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

98

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

101

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

104

105

106 **What are the possible side effects of ELOXATIN?**

107

108 **ELOXATIN can cause allergic reactions.**

109

110 **Get emergency help right away if:**

111

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

114

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

116

- 117 • Other signs of allergic reaction
  - 118 - Rash
  - 119 - Hives
  - 120 - Swelling of your lips or tongue
  - 121 - Sudden cough

122

123 **Call your doctor if you get any of the following:**

124

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

- 132 - thirst
- 133 - dry mouth
- 134 - lightheadedness (dizziness)
- 135 - decreased urination

136  
137 **Tell your doctor** if you get a dry cough and have trouble breathing (shortness of  
138 breath) before your next treatment. These may be signs of a serious lung disease.

139  
140 ELOXATIN can affect how your nerves work and make you feel (peripheral  
141 neuropathy). Tell your doctor right away, if you get any signs of nerve problems  
142 listed below:

- 143
- 144 • very sensitive to cold temperatures and cold objects
- 145 • trouble breathing, swallowing, or saying words, jaw tightness, odd feelings in  
146 your tongue, or chest pressure
- 147 • pain, tingling, burning, (pins and needles, numb feeling) in your hands, feet, or  
148 around your mouth or throat, which may cause problems walking or  
149 performing activities of daily living

150  
151 The first signs of nerve problems may occur with the initial treatment. The nerve  
152 problems can also start up to 2 days afterwards. If you develop nerve problems, the  
153 amount of ELOXATIN in your next treatment may be changed.

154  
155 For information on ways to lessen or help with the nerve problems see the end of this  
156 leaflet, "How I can help reduce the side effects caused by cold temperatures?"  
157 Other common side effects from ELOXATIN include nausea, vomiting, diarrhea,  
158 constipation, mouth sores, stomach pain, fever, loss of appetite, and tiredness.

159  
160 These are not all the possible side effects of ELOXATIN. For more information, ask  
161 your doctor or pharmacist.

#### 162 163 164 **How can I reduce the side effects caused by cold temperatures?**

- 165
- 166 • Cover yourself with a blanket while you are getting your ELOXATIN  
167 infusion.
- 168 • Do not breathe deeply when exposed to cold air.
- 169 • Wear warm clothing in cold weather at all times. Cover your mouth and  
170 nose with a scarf or a pull-down cap (ski cap) to warm the air that goes to  
171 your lungs.
- 172 • Don't take things from the freezer or refrigerator without wearing gloves.
- 173 • Drink fluids warm or at room temperature.
- 174 • Always drink through a straw.
- 175 • **Do not** use ice chips if you have nausea or mouth sores. Ask your nurse  
176 about what you can use.

- 177
- 178
- 179
- 180
- 181
- 182
- 183
- 184
- 185
- 186
- 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.

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

189  
190

191 **General information about the safe and effective use of ELOXATIN.**

192  
193  
194  
195

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

196  
197  
198  
199

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.

200  
201  
202  
203  
204

CAMPTOSAR® is a registered trademark of Pharmacia.

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

Size: 1.95" x 1.812" x 3.125

Scale: 100%

Colors: CMK

Pms 289 CV

x = .01

Date: 6/12/02

EXP  
LOT

FOR INTRAVENOUS USE ONLY  
SINGLE USE VIAL

**100 mg**  
(oxaliplatin for injection)

**ELOXATIN**

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

**ELOXATIN**<sup>™</sup>  
(oxaliplatin for injection)  
**100 mg**

---

**FOR INTRAVENOUS USE ONLY  
SINGLE USE VIAL**

Sterile Lyophilized Powder -  
Preservative Free

Must be reconstituted and  
diluted before use.

**DO NOT RECONSTITUTE  
WITH SODIUM CHLORIDE/  
CHLORIDE-CONTAINING  
SOLUTIONS**

sanofi-synthelabo

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

Dosage and Administration:  
See package insert.

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

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

**Discard Unused Portion**  
(see package insert for storage of  
reconstituted and diluted solu-  
tions)

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

**ELOXATIN**<sup>™</sup>  
(oxaliplatin for injection)  
**100 mg**

---

**FOR INTRAVENOUS USE ONLY  
SINGLE USE VIAL**

Sterile Lyophilized Powder -  
Preservative Free

Must be reconstituted and  
diluted before use.

**DO NOT RECONSTITUTE  
WITH SODIUM CHLORIDE/  
CHLORIDE-CONTAINING  
SOLUTIONS**

**Rx only**

sanofi-synthelabo

For inquiries call 1-800-446-6267  
Attn: for Sanofi-Synthelabo Inc.  
New York, NY 10016  
by Ben Venue Laboratories  
Bedford, Ohio 44146-0568  
Made in USA  
ELOXATIN is a trademark  
of Sanofi-Synthelabo

HPM03578-01-0602  
0024059704-2182



N 3 00240 59704 0  
2182



HPM03578-01



E-184 NDC 0024-0697-04 100 mg

# Eloxatin™

(oxaliplatin for injection)

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

Single Dose Vial of Powder, Preservative Free  
Must be reconstituted and diluted before use.  
DO NOT RECONSTITUTE WITH SODIUM CHLORIDE  
SOLUTIONS CONTAINING SULFONAMIDES.

Roche  
roche-synlabo

Roche for Synlab-Synlabo, Inc.  
New York, NY 10016  
Roche Vitamins Laboratories  
Route 208, Kenilworth, NJ 07033  
Roche, CH-4002, Basel, Switzerland  
Made in USA  
ELOXATIN is a trademark of Synlab-Synlabo.  
For inquiries, call 1-800-445-6535.  
HPG3387-01 00240697-04-2181

Each vial contains oxaliplatin (100 mg, active ingredient), NF 300 mg.  
Diluent: normal saline, NF 300 mg.  
See package insert.  
Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [see USP Controlled Room Temperature].  
Protect from light.  
Do not use if the seal is broken or if the vial contains a string of beads.  
Do not use if the vial contains a string of beads.  
Do not use if the vial contains a string of beads.  
Do not use if the vial contains a string of beads.

HPG3387-01  
2181



Scale: 100%  
Size: 1.5 x 4.5 in.  
CANON  
Pms 289 CV  
x = .0095  
Date: 6/12/02

LOT  
EXP

E-182 NDC 0024-0596-02 50 mg

**Eloxatin™**  
(oxaliplatin for injection)

50 mg FOR INTRAVENOUS USE ONLY  
SINGLE USE VIAL

Sterile Lyophilized Powder - Preservative Free  
Must be reconstituted and diluted before use.

HPG33396-01  
LOT  
E23



HPG33396-01  
2181

Each vial contains oxaliplatin (50 mg) lyophilized in 5 mL of water. See package insert for dosage and administration. Store at 25° C (77° F) for excursions permitted by USP <107> (see USP <107>). See USP Controlled Room Temperature. Oxidized (used beyond expiration date) and diluted solutions are not recommended for use.

Scale: 100%  
Size: 1.375 x 4.5 in.  
CN 1 K  
Vols 289 CV  
# .0095  
Date: 6/12/02