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2 **ELOXATIN™**
3 **(oxaliplatin for injection)**
4

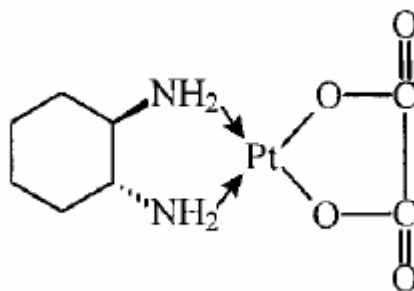
5 **WARNING**

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

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

13
14 **DESCRIPTION**

15 ELOXATIN™ (oxaliplatin for injection) is an antineoplastic agent with the molecular formula
16 C₈H₁₄N₂O₄Pt and the chemical name of *cis*-[(1 *R*,2 *R*)-1,2-cyclohexanediamine-*N,N'*] [oxalato(2-
17)- *O,O'*] platinum. Oxaliplatin is an organoplatinum complex in which the platinum atom is
18 complexed with 1,2-diaminocyclohexane(DACH) and with an oxalate ligand as a leaving group.
19



20
21
22 The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly
23 soluble in methanol, and practically insoluble in ethanol and acetone. ELOXATIN is supplied in
24 vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder
25 for reconstitution. Lactose monohydrate is present as an inactive ingredient at 450 mg and 900
26 mg in the 50 mg and 100 mg dosage strengths, respectively.

27
28 **CLINICAL PHARMACOLOGY**
29

30 **Mechanism of Action**

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

38

39 **Pharmacology**

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

44

45 **Human Pharmacokinetics**

46 The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma
47 ultrafiltrate. The decline of ultrafilterable platinum levels following oxaliplatin administration is
48 triphasic, characterized by two relatively short distribution phases ($t_{1/2\alpha}$; 0.43 hours and $t_{1/2\beta}$; 16.8
49 hours) and a long terminal elimination phase ($t_{1/2\gamma}$; 391 hours). Pharmacokinetic parameters
50 obtained after a single 2-hour IV infusion of ELOXATIN at a dose of 85 mg/m² expressed as
51 ultrafilterable platinum were C_{\max} of 0.814 μg/mL and volume of distribution of 440 L.

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

56

57 **Distribution**

58 At the end of a 2-hour infusion of ELOXATIN, approximately 15% of the administered platinum
59 is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or
60 eliminated in the urine. In patients, plasma protein binding of platinum is irreversible and is
61 greater than 90%. The main binding proteins are albumin and gamma-globulins. Platinum also
62 binds irreversibly and accumulates (approximately 2-fold) in erythrocytes, where it appears to
63 have no relevant activity. No platinum accumulation was observed in plasma ultrafiltrate
64 following 85 mg/m² every two weeks.

65

66 **Metabolism**

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

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

73

74 **Elimination**

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

82

83 **Pharmacokinetics in Special Populations**

84 **Renal Impairment**

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

90 **Drug - Drug Interactions**

91 No pharmacokinetic interaction between 85 mg/m² of ELOXATIN and infusional 5-FU has been
92 observed in patients treated every 2 weeks, but increases of 5-FU plasma concentrations by
93 approximately 20% have been observed with doses of 130 mg/m² of ELOXATIN administered
94 every 3 weeks. *In vitro*, platinum was not displaced from plasma proteins by the following
95 medications: erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel. *In vitro*,
96 oxaliplatin is not metabolized by, nor does it inhibit, human cytochrome P450 isoenzymes. No
97 P450-mediated drug-drug interactions are therefore anticipated in patients.

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

101

102 **CLINICAL STUDIES**

103 **Combination Adjuvant Therapy with ELOXATIN and infusional 5-FU/LV in Patients** 104 **with Stage II or III Colon Cancer**

105 An international, multicenter, randomized study compared the efficacy and evaluated the safety
106 of ELOXATIN in combination with an infusional schedule of 5-FU/LV to infusional 5-FU/LV
107 alone, in patients with stage II (Dukes' B2) or III (Dukes' C) colon cancer who had undergone
108 complete resection of the primary tumor. The primary objective of the study was to compare the
109 3-year disease-free survival (DFS) in patients receiving ELOXATIN and infusional 5-FU/LV to

110 those receiving 5-FU/LV alone. Patients were to be treated for a total of 6 months (i.e., 12
 111 cycles). A total of 2246 patients were randomized; 1123 patients per study arm. Patients in the
 112 study had to be between 18 and 75 years of age, have histologically proven stage II (T₃-T₄ N₀
 113 M₀; Dukes' B₂) or III (any T N₁₋₂ M₀; Dukes' C) colon carcinoma (with the inferior pole of the
 114 tumor above the peritoneal reflection, i.e., ≥15 cm from the anal margin) and undergone (within 7
 115 weeks prior to randomization) complete resection of the primary tumor without gross or
 116 microscopic evidence of residual disease. Patients had to have had no prior chemotherapy,
 117 immunotherapy or radiotherapy, and have an ECOG performance status of 0,1, or 2 (KPS ≥
 118 60%), absolute neutrophil count (ANC) > 1.5x10⁹/L, platelets ≥100x10⁹/L, serum creatinine ≤
 119 1.25 x ULN total bilirubin < 2 x ULN, AST/ALT < 2 x ULN and carcino-embryogenic antigen
 120 (CEA) < 10 ng/mL. Patients with preexisting peripheral neuropathy (NCI grade ≥ 1) were
 121 ineligible for this trial.

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

123 **Table 1 - Dosing Regimens in Adjuvant Therapy Study**
 124

Treatment Arm	Dose	Regimen
ELOXATIN + 5-FU/LV FOLFOX4 (N =1123)	Day 1: ELOXATIN: 85 mg/m² (2-hour infusion) + LV: 200 mg/m² (2-hour infusion), followed by 5-FU: 400 mg/m² (bolus), 600 mg/m² (22-hour infusion) Day 2: LV: 200 mg/m² (2-hour infusion), followed by 5-FU: 400 mg/m² (bolus), 600 mg/m² (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

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

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129 **Table 2 - Patient Characteristics in Adjuvant Therapy Study**
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	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 caecum	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

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Table 3 - 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

136

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

139

Table 4 - Summary of DFS analysis

140

[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	

141 *For patients alive or lost to follow-up

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

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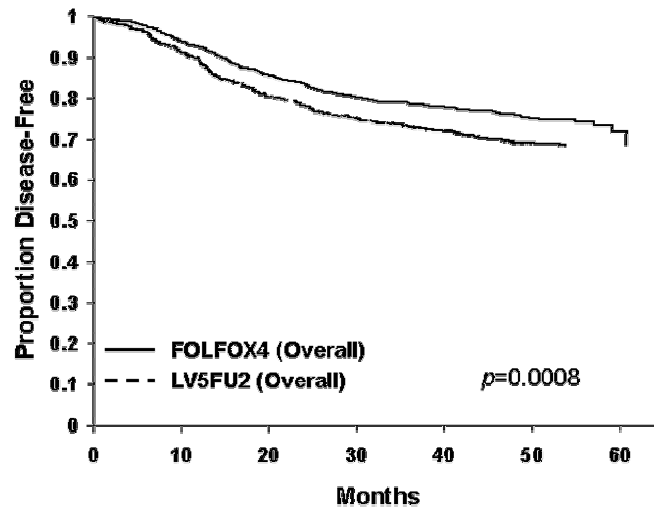
147 Figure 1 shows the Kaplan-Meier DFS curves for the comparison of ELOXATIN and infusional
148 5-FU/LV combination and infusional 5-FU/LV alone for the overall population (ITT analysis).
149 Figure 2 shows the Kaplan-Meier DFS curves for the comparison of ELOXATIN and infusional
150 5-FU/LV combination and infusional 5-FU/LV alone for the Stage III Subgroup.

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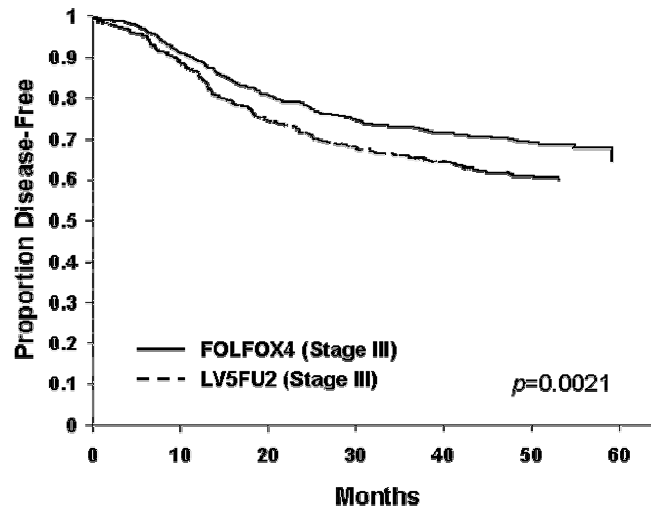
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163 **Figure 1 - Kaplan-Meier DFS curves by treatment arm for Overall Population**

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176 **Figure 2 - Kaplan-Meier DFS curves by treatment arm for Stage III Subgroup**

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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.

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

188 **Combination Therapy with ELOXATIN and 5-FU/LV in Patients Previously Untreated for**
 189 **Advanced Colorectal Cancer**

190 A North American, multicenter, open-label, randomized controlled study was sponsored by the
 191 National Cancer Institute (NCI) as an intergroup study led by the North Central Cancer
 192 Treatment Group (NCCTG). The study had 7 arms at different times during its conduct, four of
 193 which were closed due to either changes in the standard of care, toxicity, or simplification.
 194 During the study, the control arm was changed to irinotecan plus 5-FU/LV. The results reported
 195 below compared the efficacy and safety of two experimental regimens, ELOXATIN in
 196 combination with infusional 5-FU/LV and a combination of ELOXATIN plus irinotecan, to an
 197 approved control regimen of irinotecan plus 5-FU/LV in 795 concurrently randomized patients
 198 previously untreated for locally advanced or metastatic colorectal cancer. After completion of
 199 enrollment, the dose of irinotecan plus 5-FU/LV was decreased due to toxicity. Patients had to
 200 be at least 18 years of age, have known locally advanced, locally recurrent, or metastatic
 201 colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy with curative
 202 intent, histologically proven colorectal adenocarcinoma, measurable or evaluable disease, with an
 203 ECOG performance status 0,1, or 2. Patients had to have granulocyte count $\geq 1.5 \times 10^9/L$,
 204 platelets $\geq 100 \times 10^9/L$, hemoglobin ≥ 9.0 gm/dL, creatinine $\leq 1.5 \times$ ULN, total bilirubin ≤ 1.5
 205 mg/dL, AST $\leq 5 \times$ ULN, and alkaline phosphatase $\leq 5 \times$ ULN. Patients may have received
 206 adjuvant therapy for resected Stage II or III disease without recurrence within 12 months. The
 207 patients were stratified for ECOG performance status (0, 1 vs. 2), prior adjuvant chemotherapy
 208 (yes vs. no), prior immunotherapy (yes vs. no), and age (<65 vs. ≥ 65 years). Although no post
 209 study treatment was specified in the protocol, 65 to 72% of patients received additional post
 210 study chemotherapy after study treatment discontinuation on all arms. Fifty-eight percent of
 211 patients on the ELOXATIN plus 5-FU/LV arm received an irinotecan-containing regimen and
 212 23% of patients on the irinotecan plus 5-FU/LV arm received oxaliplatin-containing regimens.
 213 Oxaliplatin was not commercially available during the trial.

214 The following table presents the dosing regimens of the three arms of the study.

215

216 **Table 5 – Dosing Regimens in Patients Previously Untreated for Advanced**
 217 **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
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219 The following table presents the demographics and dosing of the patient population entered into
220 this study.

221

222 **Table 6 – Patient Demographics and Dosing in Patients Previously Untreated for**
223 **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

224

225 The length of a treatment cycle was 2 weeks for the ELOXATIN and 5-FU/LV regimen; 6 weeks
226 for the irinotecan plus 5-FU/LV regimen; and 3 weeks for the ELOXATIN plus irinotecan

227 regimen. The median number of cycles administered per patient was 10 (23.9 weeks) for the
 228 ELOXATIN and 5-FU/LV regimen, 4 (23.6 weeks) for the irinotecan plus 5-FU/LV regimen, and
 229 7 (21.0 weeks) for the ELOXATIN plus irinotecan regimen. Patients treated with the
 230 ELOXATIN and 5-FU/LV combination had a significantly longer time to tumor progression
 231 based on investigator assessment, longer overall survival, and a significantly higher confirmed
 232 response rate based on investigator assessment compared to patients given irinotecan plus 5-
 233 FU/LV. The following table summarizes the efficacy results.

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235

Table 7 – Summary of Efficacy

	ELOXATIN + 5-FU/LV N=267	irinotecan + 5-FU/LV N=264	ELOXATIN + irinotecan N=264
Survival (ITT)			
Number of deaths N (%)	155 (58.1)	192 (72.7)	175 (66.3)
Median survival (months)	19.4	14.6	17.6
Hazard Ratio and (95% confidence interval)	0.65 (0.53-0.80)*		
P-value	<0.0001*	-	-
TTP (ITT, investigator assessment)			
Percentage of progressors	82.8	81.8	89.4
Median TTP (months)	8.7	6.9	6.5
Hazard Ratio and (95% confidence interval)	0.74 (0.61-0.89)*		
P-value	0.0014*	-	-
Response Rate (investigator assessment)**			
Patients with measurable disease	210	212	215
Complete response N (%)	13 (6.2)	5 (2.4)	7 (3.3)
Partial response N (%)	82 (39.0)	64 (30.2)	67 (31.2)
Complete and partial response N (%)	95 (45.2)	69 (32.5)	74 (34.4)
95% confidence interval	(38.5 – 52.0)	(26.2 – 38.9)	(28.1 – 40.8)
P-value	0.0080*	-	-

236

*Compared to irinotecan plus 5-FU/LV (IFL) arm

237

**Based on all patients with measurable disease at baseline

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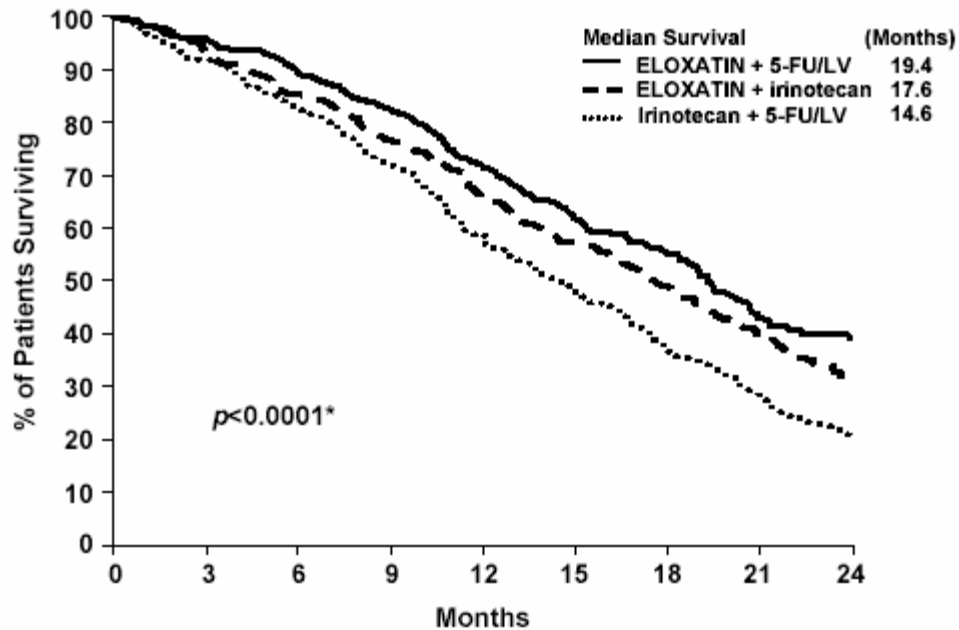
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The numbers in the response rate and TTP analysis are based on unblinded investigator
 240 assessment.

241

242

Figure 3 illustrates the Kaplan-Meier survival curves for the comparison of ELOXATIN and 5-
 243 FU/LV combination and ELOXATIN plus irinotecan to irinotecan plus 5-FU/LV.



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

244

245

Figure 3 - Kaplan-Meier Overall Survival by treatment arm

246

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

252

253 **Combination Therapy with ELOXATIN and 5-FU/LV in Previously Treated Patients with**
 254 **Advanced Colorectal Cancer**

255 A multicenter, open-label, randomized, three-arm controlled study was conducted in the US and
 256 Canada comparing the efficacy and safety of ELOXATIN in combination with an infusional
 257 schedule of 5-FU/LV to the same dose and schedule of 5-FU/LV alone and to single agent
 258 oxaliplatin in patients with advanced colorectal cancer who had relapsed/progressed during or
 259 within 6 months of first-line therapy with bolus 5-FU/LV and irinotecan. The study was intended
 260 to be analyzed for response rate after 450 patients were enrolled. Survival will be subsequently
 261 assessed in all patients enrolled in the completed study. Accrual to this study is complete, with
 262 821 patients enrolled. Patients in the study had to be at least 18 years of age, have unresectable,
 263 measurable, histologically proven colorectal adenocarcinoma, with a Karnofsky performance
 264 status >50%. Patients had to have SGOT(AST) and SGPT(ALT) ≤2x the institution's upper limit
 265 of normal (ULN), unless liver metastases were present and documented at baseline by CT or MRI
 266 scan, in which case ≤5x ULN was permitted. Patients had to have alkaline phosphatase ≤2x the
 267 institution's ULN, unless liver metastases were present and documented at baseline by CT or

268 MRI scan, in which cases $\leq 5x$ ULN was permitted. Prior radiotherapy was permitted if it had
 269 been completed at least 3 weeks before randomization.

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

271

272 **Table 8 – Dosing Regimens in Refractory and Relapsed Colorectal Cancer Clinical**
 273 **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

274

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

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

282

283 **Table 9 – Patient Demographics in Refractory and Relapsed Colorectal Cancer**
 284 **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

285

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

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

291

292

Table 10 - 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%

293

294

295

Table 11 - 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

296

297

298

*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.

299

300

301

302

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.

303

304

305

306

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.

307

308 **INDICATIONS AND USAGE**

309

310 ELOXATIN, used in combination with infusional 5-FU/LV, is indicated for adjuvant treatment
311 of stage III colon cancer patients who have undergone complete resection of the primary tumor.
312 The indication is based on an improvement in disease-free survival, with no demonstrated benefit
313 in overall survival after a median follow up of 4 years.

314

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

317

318 **CONTRAINDICATIONS**

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

321

322 **WARNINGS**

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

330

331 **Pregnancy Category D**

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

341

342 **PRECAUTIONS**

343 **General**

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

348

349 **Neuropathy**

350

351 **Patients with Stage II or III Colon Cancer**

352

353 Neuropathy was graded using a prelisted module derived from the Neuro-Sensory section of the
354 NCI CTC scale version 1, as follows:

355

356 **Table 12 - NCI CTC Grading for Neuropathy in Adjuvant Patients**

NCI 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

357

358 Peripheral sensory neuropathy was reported in adjuvant patients treated with the ELOXATIN
359 combination with a frequency of 92% (all grades) and 13% (grade 3). At the 28-day follow up
360 after the last treatment cycle, 60% of all patients had any grade (Grade 1=39.6%, Grade
361 2=15.7%, Grade 3=5.0%) peripheral sensory neuropathy decreasing to 39% at 6 months follow-
362 up (Grade 1=30.5%, Grade 2=7.4%, Grade 3=1.3%) and 21% at 18 months of follow-up (Grade
363 1=17.2%, Grade 2=3.0%, Grade 3=0.5%).

364

365 **Previously Untreated and Previously Treated Patients with Advanced Colorectal**
366 **Cancer**

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

369 In the previously treated study, neuropathy information was collected to establish that
370 ELOXATIN is associated with two types of neuropathy:

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

383 An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% (grade 3/4) of patients
384 previously untreated for advanced colorectal cancer, and the previously treated patients, is

385 characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or
386 bronchospasm (no stridor or wheezing).

387 • **A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually**
388 **characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits**
389 **in proprioception that can interfere with daily activities (e.g., writing, buttoning,**
390 **swallowing, and difficulty walking from impaired proprioception).** These forms of
391 neuropathy occurred in 48% of the study patients receiving ELOXATIN with 5-FU/LV.
392 Persistent neuropathy can occur without any prior acute neuropathy event. The majority of
393 the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade
394 1 or 2 events. These symptoms may improve in some patients upon discontinuation of
395 ELOXATIN.

396 **Overall, neuropathy was reported in patients previously untreated for advanced colorectal**
397 **cancer in 82% (all grades) and 19% (grade 3/4), and in the previously treated patients in**
398 **74% (all grades) and 7% (grade 3/4) events. Information regarding reversibility of**
399 **neuropathy was not available from the trial for patients who had not been previously**
400 **treated for colorectal cancer.**

401 **Neurotoxicity scale:**

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

406

407 **Pulmonary Toxicity**

408 ELOXATIN has been associated with pulmonary fibrosis (<1% of study patients), which may be
409 fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (grade 3)
410 with no grade 4 events in the ELOXATIN plus infusional 5-FU/LV arm compared to 4.5% (any
411 grade) and no grade 3 and 0.1% grade 4 events in the infusional 5-FU/LV alone arm in adjuvant
412 colon cancer patients. In this study, one patient died from eosinophilic pneumonia in the
413 ELOXATIN combination arm. The combined incidence of cough, dyspnea and hypoxia was 43%
414 (any grade) and 7% (grade 3 and 4) in the ELOXATIN plus 5-FU/LV arm compared to 32% (any
415 grade) and 5% (grade 3 and 4) in the irinotecan plus 5-FU/LV arm of unknown duration for
416 patients with previously untreated colorectal cancer. In case of unexplained respiratory
417 symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates,
418 ELOXATIN should be discontinued until further pulmonary investigation excludes interstitial
419 lung disease or pulmonary fibrosis.

420 **Hepatotoxicity**

421 Hepatotoxicity as evidenced in the adjuvant study by increase in transaminases (57% vs. 34%)
422 and alkaline phosphatase (42% vs. 20%) was observed more commonly in the ELOXATIN
423 combination arm. The incidence of increased bilirubin was similar on both arms. Changes noted
424 on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations,
425 perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be

426 considered, and if appropriate, should be investigated in case of abnormal liver function test
427 results or portal hypertension, which cannot be explained by liver metastases.

428 **Information for Patients**

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

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

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

440

441 **Laboratory Tests**

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

445

446 **Laboratory Test Interactions**

447 None known.

448

449 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

455 In a fertility study, male rats were given oxaliplatin at 0, 0.5, 1, or 2 mg/kg/day for five days
456 every 21 days for a total of three cycles prior to mating with females that received two cycles of
457 oxaliplatin on the same schedule. A dose of 2 mg/kg/day (less than one-seventh the
458 recommended human dose on a body surface area basis) did not affect pregnancy rate, but caused
459 developmental mortality (increased early resorptions, decreased live fetuses, decreased live
460 births) and delayed growth (decreased fetal weight).

461 Testicular damage, characterized by degeneration, hypoplasia, and atrophy, was observed in dogs
462 administered oxaliplatin at 0.75 mg/kg/day x 5 days every 28 days for three cycles. A no effect
463 level was not identified. This daily dose is approximately one-sixth of the recommended human
464 dose on a body surface area basis.

465

466 **Pregnancy Category D - See WARNINGS**

467

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

473

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

476

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

485

486 **Geriatric Use** - No significant effect of age on the clearance of ultrafilterable platinum has been
487 observed. In the adjuvant therapy colon cancer randomized clinical trial, (see CLINICAL
488 STUDIES) 723 patients treated with ELOXATIN and infusional 5-FU/LV were < 65 years and
489 400 patients were ≥ 65 years. In the previously untreated for advanced colorectal cancer
490 randomized clinical trial (see CLINICAL STUDIES) of ELOXATIN, 160 patients treated with
491 ELOXATIN and 5-FU/LV were < 65 years and 99 patients were ≥65 years. The same efficacy
492 improvements in response rate, time to tumor progression, and overall survival were observed in
493 the ≥65 year old patients as in the overall study population. In the previously treated randomized
494 clinical trial (see CLINICAL STUDIES) of ELOXATIN, 95 patients treated with ELOXATIN
495 and 5-FU/LV were < 65 years and 55 patients were ≥65 years. The rates of overall adverse
496 events, including grade 3 and 4 events, were similar across and within arms in the different age
497 groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, leukopenia, fatigue and
498 syncope were higher in patients ≥65 years old. No adjustment to starting dose was required in
499 patients ≥65 years old.

500 **Drug Interactions** - No specific cytochrome P-450-based drug interaction studies have been
501 conducted. No pharmacokinetic interaction between 85 mg/m² ELOXATIN and 5-FU/LV has
502 been observed in patients treated every 2 weeks. Increases of 5-FU plasma concentrations by
503 approximately 20% have been observed with doses of 130 mg/m² ELOXATIN dosed every 3
504 weeks. Since platinum-containing species are eliminated primarily through the kidney, clearance
505 of these products may be decreased by coadministration of potentially nephrotoxic compounds;
506 although, this has not been specifically studied (see CLINICAL PHARMACOLOGY).

507

508 **ADVERSE REACTIONS**

509 More than 1100 patients with stage II or III colon cancer and more than 4,000 patients with
510 advanced colorectal cancer have been treated in clinical studies with ELOXATIN either as a
511 single agent or in combination with other medications. The most common adverse reactions in
512 patients with stage II or III colon cancer receiving adjuvant therapy, were peripheral sensory
513 neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and
514 alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. The most common adverse
515 reactions in previously untreated and treated patients were peripheral sensory neuropathies,
516 fatigue, neutropenia, nausea, emesis, and diarrhea (see PRECAUTIONS).
517

518 **Combination Adjuvant Therapy with ELOXATIN and infusional 5-FU/LV in Patients**
519 **with Stage II or III Colon Cancer**

520
521 One thousand one hundred and eight patients with stage II or III colon cancer, who had
522 undergone complete resection of the primary tumor, have been treated in a clinical study with
523 ELOXATIN in combination with infusional 5-FU/LV (See CLINICAL STUDIES). The
524 incidence of grade 3 or 4 adverse events was 70% on the ELOXATIN combination arm, and 31%
525 on the infusional 5-FU/LV arm. The adverse reactions in this trial are shown in the tables below.
526 Discontinuation of treatment due to adverse events occurred in 15% of the patients receiving
527 ELOXATIN and infusional 5-FU/LV. Both 5-FU/LV and ELOXATIN are associated with
528 gastrointestinal or hematologic adverse events. When ELOXATIN is administered in
529 combination with infusional 5-FU/LV, the incidence of these events is increased.
530

531 The incidence of death within 28 days of last treatment, regardless of causality, was 0.5% (n=6)
532 in both the ELOXATIN combination and infusional 5-FU/LV arms, respectively. Deaths within
533 60 days from initiation of therapy were 0.3% (n=3) in both the ELOXATIN combination and
534 infusional 5-FU/LV arms, respectively. On the ELOXATIN combination arm, 3 deaths were due
535 to sepsis/neutropenic sepsis, 2 from intracerebral bleeding and one from eosinophilic pneumonia.
536 On the 5-FU/LV arm, one death was due to suicide, 2 from Steven-Johnson Syndrome (1 patient
537 also had sepsis), 1 unknown cause, 1 anoxic cerebral infarction and 1 probable abdominal aorta
538 rupture.
539

540 The following table provides adverse events reported in the adjuvant therapy colon cancer
541 clinical trial (see CLINICAL STUDIES) by body system and decreasing order of frequency in
542 the ELOXATIN and infusional 5-FU/LV arm for events with overall incidences $\geq 5\%$ and for
543 NCI grade 3/4 events with incidences $\geq 1\%$. This table does not include hematologic and blood
544 chemistry abnormalities; these are shown separately below.
545

546 **Table 13 - Adverse Experiences Reported in Patients with Stage II or III Colon**
547 **Cancer receiving Adjuvant Treatment ($\geq 5\%$ of all patients and with $\geq 1\%$ NCI Grade**
548 **3/4 events)**

549

Adverse Event (WHO/Pref)+	ELOXATIN + 5-FU/LV N=1108		5-FU/LV N=1111	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any Event	100	70	99	31
Allergy/Immunology				
Allergic Reaction	10	3	2	<1
Constitutional Symptoms/Pain				
Fatigue	44	4	38	1
Abdominal Pain	18	1	17	2
Dermatology/Skin				
Skin Disorder	32	2	36	2
Injection Site Reaction ¹	11	3	10	3
Gastrointestinal				
Nausea	74	5	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) by body system and decreasing order of frequency in the ELOXATIN and infusional 5-FU/LV arm for events with overall incidences $\geq 5\%$ but with incidences $<1\%$ NCI grade 3/4 events.

Table 14 - Adverse Experiences Reported in Patients with Stage II or III Colon Cancer receiving Adjuvant Treatment ($\geq 5\%$ 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

564

565 Although specific events can vary, the overall frequency of adverse events was similar in men
566 and women and in patients <65 and ≥65 years. However, the following grade 3/4 events were
567 more common in females: diarrhea, fatigue, granulocytopenia, nausea and vomiting. In patients
568 ≥65 years old, the incidence of grade 3/4 diarrhea and granulocytopenia was higher than in
569 younger patients. Insufficient subgroup sizes prevented analysis of safety by race. The following
570 additional adverse events, were reported in ≥2% and <5% of the patients in the ELOXATIN and
571 infusional 5-FU/LV combination arm (listed in decreasing order of frequency): pain, leukopenia,
572 weight decrease, coughing.

573

574 **Patients Previously Untreated for Advanced Colorectal Cancer**

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

579 Both 5-FU and ELOXATIN are associated with gastrointestinal and hematologic adverse events.
580 When ELOXATIN is administered in combination with 5-FU, the incidence of these events is
581 increased.

582 The incidence of death within 30 days of treatment in the previously untreated for advanced
583 colorectal cancer study, regardless of causality, was 3% with the ELOXATIN and 5-FU/LV
584 combination, 5% with irinotecan plus 5-FU/LV, and 3% with ELOXATIN plus irinotecan.
585 Deaths within 60 days from initiation of therapy were 2.3% with the ELOXATIN and 5-FU/LV
586 combination, 5.1% with irinotecan plus 5-FU/LV, and 3.1% with ELOXATIN plus irinotecan.

587 The following table provides adverse events reported in the previously untreated for advanced
588 colorectal cancer study (see CLINICAL STUDIES) by body system and decreasing order of
589 frequency in the ELOXATIN and 5-FU/LV combination arm for events with overall incidences
590 $\geq 5\%$ and for grade 3/4 events with incidences $\geq 1\%$. This table does not include hematologic and
591 blood chemistry abnormalities; these are shown separately below.

592

593 **Table 15 – Adverse Experience Reported in Patients Previously Untreated for**
594 **Advanced Colorectal Cancer Clinical Trial ($\geq 5\%$ of all patients and with $\geq 1\%$ NCI**
595 **Grade 3/4 events)**

	ELOXATIN + 5-FU/LV N=259		irinotecan + 5-FU/LV N=256		ELOXATIN + irinotecan N=258	
Adverse Event (WHO/Pref)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any Event	99	82	98	70	99	76
Allergy/Immunology						
Hypersensitivity	12	2	5	0	6	1
Cardiovascular						
Thrombosis	6	5	6	6	3	3
Hypotension	5	3	6	3	4	3
Constitutional Symptoms/Pain/Ocular/Visual						
Fatigue	70	7	58	11	66	16
Abdominal Pain	29	8	31	7	39	10
Myalgia	14	2	6	0	9	2
Pain	7	1	5	1	6	1
Vision abnormal	5	0	2	1	6	1
Neuralgia	5	0	0	0	2	1
Dermatology/Skin						
Skin reaction – hand/foot	7	1	2	1	1	0
Injection site reaction	6	0	1	0	4	1
Gastrointestinal						
Nausea	71	6	67	15	83	19
Diarrhea	56	12	65	29	76	25
Vomiting	41	4	43	13	64	23
Stomatitis	38	0	25	1	19	1
Anorexia	35	2	25	4	27	5
Constipation	32	4	27	2	21	2
Diarrhea-colostomy	13	2	16	7	16	3
Gastrointestinal NOS	5	2	4	2	3	2
Hematology/Infection						
Infection no ANC	10	4	5	1	7	2
Infection –ANC	8	8	12	11	9	8
Lymphopenia	6	2	4	1	5	2
Febrile neutropenia	4	4	15	14	12	11
Hepatic/Metabolic/Laboratory/Renal						
Hyperglycemia	14	2	11	3	12	3
Hypokalemia	11	3	7	4	6	2
Dehydration	9	5	16	11	14	7

Adverse Event (WHO/Pref)	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 (%)
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

596

597 The following table provides adverse events reported in the previously untreated for advanced
598 colorectal cancer study (see CLINICAL STUDIES) by body system and decreasing order of
599 frequency in the ELOXATIN and 5-FU/LV combination arm for events with overall incidences
600 $\geq 5\%$ but with incidences $< 1\%$ NCI Grade 3/4 events.

601

602 **Table 16 - Adverse Experience Reported in Patients Previously Untreated for**
603 **Advanced Colorectal Cancer Clinical Trial ($\geq 5\%$ of all patients but with $< 1\%$ NCI**
604 **Grade 3/4 events)**

Adverse Event (WHO/Pref)	ELOXATIN + 5-FU/LV N=259	irinotecan + 5-FU/LV N=256	ELOXATIN + irinotecan N=258
	All Grades (%)	All Grades (%)	All Grades (%)
Allergy/Immunology			
Rash	11	4	7
Rhinitis allergic	10	6	6
Cardiovascular			
Edema	15	13	10
Constitutional Symptoms/Pain/Ocular/Visual			
Headache	13	6	9
Weight loss	11	9	11
Epistaxis	10	2	2
Tearing	9	1	2
Rigors	8	2	7
Dysphasia	5	3	3
Sweating	5	6	12
Arthralgia	5	5	8
Dermatology/Skin			
Alopecia	38	44	67
Flushing	7	2	5
Pruritis	6	4	2
Dry Skin	6	2	5
Gastrointestinal			
Taste perversion	14	6	8
Dyspepsia	12	7	5
Flatulence	9	6	5
Mouth Dryness	5	2	3
Hematology/Infection			
Fever no ANC	16	9	9
Hepatic/Metabolic/Laboratory/Renal			
Hypocalcemia	7	5	4
Elevated Creatinine	4	4	5
Neurology			
Insomnia	13	9	11
Depression	9	5	7
Dizziness	8	6	10
Anxiety	5	2	6

605

606 Adverse events were similar in men and women and in patients <65 and ≥65 years, but older
607 patients may have been more susceptible to diarrhea, dehydration, hypokalemia, leukopenia,
608 fatigue and syncope. The following additional adverse events, at least possibly related to
609 treatment and potentially important, were reported in ≥2% and <5% of the patients in the
610 ELOXATIN and 5-FU/LV combination arm (listed in decreasing order of frequency): metabolic,
611 pneumonitis, catheter infection, vertigo, prothrombin time, pulmonary, rectal bleeding, dysuria,
612 nail changes, chest pain, rectal pain, syncope, hypertension, hypoxia, unknown infection, bone
613 pain, pigmentation changes, and urticaria.

614

615 **Previously Treated Patients with Advanced Colorectal Cancer**

616 Four hundred and fifty patients (about 150 receiving the combination of ELOXATIN and 5-
617 FU/LV) were studied in a randomized trial in patients with refractory and relapsed colorectal
618 cancer (see CLINICAL STUDIES). The adverse event profile in this study was similar to that
619 seen in other studies and the adverse reactions in this trial are shown in the tables below.

620 Thirteen percent of patients in the ELOXATIN and 5-FU/LV combination arm and 18% in the 5-
621 FU/LV arm of the previously treated study had to discontinue treatment because of adverse
622 effects related to gastrointestinal, or hematologic adverse events, or neuropathies. Both 5-FU and
623 ELOXATIN are associated with gastrointestinal and hematologic adverse events. When
624 ELOXATIN is administered in combination with 5-FU, the incidence of these events is
625 increased.

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

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

636

637 **Table 17 – Adverse Experience Reported In Previously Treated Colorectal Cancer** 638 **Clinical Trial (≥5% of all patients and with ≥1% NCI Grade 3/4 events)**

	5-FU/LV (N = 142)		ELOXATIN (N = 153)		ELOXATIN + 5-FU/LV (N = 150)	
Adverse Event (WHO/Pref)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any Event	98	41	100	46	99	73
Cardiovascular						
Dyspnea	11	2	13	7	20	4
Coughing	9	0	11	0	19	1
Edema	13	1	10	1	15	1
Thromboembolism	4	2	2	1	9	8
Chest Pain	4	1	5	1	8	1
Constitutional Symptoms/Pain						
Fatigue	52	6	61	9	68	7
Back Pain	16	4	11	0	19	3
Pain	9	3	14	3	15	2
Dermatology/Skin						
Injection Site Reaction	5	1	9	0	10	3
Gastrointestinal						
Diarrhea	44	3	46	4	67	11
Nausea	59	4	64	4	65	11
Vomiting	27	4	37	4	40	9
Stomatitis	32	3	14	0	37	3
Abdominal Pain	31	5	31	7	33	4
Anorexia	20	1	20	2	29	3
Gastroesophageal Reflux	3	0	1	0	5	2
Hematology/Infection						
Fever	23	1	25	1	29	1
Febrile Neutropenia	1	1	0	0	6	6
Hepatic/Metabolic/Laboratory/Renal						
Hypokalemia	3	1	3	2	9	4
Dehydration	6	4	5	3	8	3
Neurology						
Neuropathy	17	0	76	7	74	7
Acute	10	0	65	5	56	2
Persistent	9	0	43	3	48	6

639

640 The following table provides adverse events reported in the previously treated study (see
641 CLINICAL STUDIES) by body system and in decreasing order of frequency in the ELOXATIN
642 and 5-FU/LV combination arm for events with overall incidences $\geq 5\%$ but with incidences $< 1\%$
643 NCI Grade 3/4 events.

644

645 **Table 18 - Adverse Experience Reported In Previously Treated Colorectal Cancer**
646 **Clinical Trial ($\geq 5\%$ of all patients but with $< 1\%$ NCI Grade 3/4 events)**

Adverse Event (WHO/Pref)	5-FU/LV (N = 142)	ELOXATIN (N = 153)	ELOXATIN + 5-FU/LV (N = 150)
	All Grades (%)	All Grades (%)	All Grades (%)
Allergy/Immunology			
Rhinitis	4	6	15
Allergic Reaction	1	3	10
Rash	5	5	9
Cardiovascular			
Peripheral Edema	11	5	10
Constitutional Symptoms/Pain/Ocular/Visual			
Headache	8	13	17
Arthralgia	10	7	10
Epistaxis	1	2	9
Abnormal Lacrimation	6	1	7
Rigors	6	9	7
Dermatology/Skin			
Hand-Foot Syndrome	13	1	11
Flushing	2	3	10
Alopecia	3	3	7
Gastrointestinal			
Constipation	23	31	32
Dyspepsia	10	7	14
Taste Perversion	1	5	13
Mucositis	10	2	7
Flatulence	6	3	5
Hepatic/Metabolic/Laboratory/Renal			
Hematuria	4	0	6
Dysuria	1	1	6
Neurology			
Dizziness	8	7	13
Insomnia	4	11	9
Pulmonary			
Upper Resp Tract Infection	4	7	10
Pharyngitis	10	2	9
Hiccup	0	2	5

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

658

659 **Hematologic**

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

664

665 **Table 19 - Adverse Hematologic Experiences in Patients with Stage II or III Colon**
 666 **Cancer Receiving Adjuvant Therapy**

667 **(≥5% of patients)**

668

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

669

670

671 **Table 20 – Adverse Hematologic Experiences in Patients Previously Untreated for**
 672 **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

673

674

675

Table 21 – 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

676

677

Thrombocytopenia

678

679

680

681

682

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.

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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.

691

692 **Neutropenia**

693 Neutropenia was frequently observed with the combination of ELOXATIN and 5-FU/LV, with
694 Grade 3 and 4 events reported in 29% and 12% of adjuvant patients with colon cancer,
695 respectively. In the adjuvant trial, 3 patients died from sepsis/neutropenic sepsis. Grade 3 and 4
696 events were reported in 35% and 18% of the patients previously untreated for advanced
697 colorectal cancer, respectively. Grade 3 and 4 events were reported in 27% and 17% of
698 previously treated patients, respectively. In adjuvant patients the incidence of either febrile
699 neutropenia (0.7%) or documented infection with concomitant grade 3/4 neutropenia (1.1%) was
700 1.8% in the ELOXATIN and 5-FU/LV arm. The incidence of febrile neutropenia in the patients
701 previously untreated for advanced colorectal cancer was 15% (3% of cycles) in the irinotecan
702 plus 5-FU/LV arm and 4% (less than 1% of cycles) in the ELOXATIN and 5-FU/LV
703 combination arm. Additionally, in this same population, infection with grade 3 or 4 neutropenia
704 was 12% in the irinotecan plus 5-FU/LV, and 8% in the ELOXATIN and 5-FU/LV combination.
705 The incidence of febrile neutropenia in the previously treated patients was 1% in the 5-FU/LV
706 arm and 6% (less than 1% of cycles) in the ELOXATIN and 5-FU/LV combination arm.

707

708 **Gastrointestinal**

709 In patients receiving the combination of ELOXATIN plus infusional 5-FU/LV for adjuvant
710 treatment for colon cancer the incidence of Grade 3/4 nausea and vomiting was greater than those
711 receiving infusional 5-FU/LV alone (see table). In patients previously untreated for advanced
712 colorectal cancer receiving the combination of ELOXATIN and 5-FU/LV, the incidence of Grade
713 3 and 4 vomiting and diarrhea was less compared to irinotecan plus 5-FU/LV controls (see table).
714 In previously treated patients receiving the combination of ELOXATIN and 5-FU/LV, the
715 incidence of Grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis increased
716 compared to 5-FU/LV controls (see table).

717 The incidence of gastrointestinal adverse events in the previously untreated and previously
718 treated patients appears to be similar across cycles. Premedication with antiemetics, including 5-
719 HT₃ blockers, is recommended. Diarrhea and mucositis may be exacerbated by the addition of
720 ELOXATIN to 5-FU/LV, and should be managed with appropriate supportive care. Since cold
721 temperature can exacerbate acute neurological symptoms, ice (mucositis prophylaxis) should be
722 avoided during the infusion of ELOXATIN.

723

724 **Dermatologic**

725 ELOXATIN did not increase the incidence of alopecia compared to 5-FU/LV alone. No
726 complete alopecia was reported. The incidence of Grade 3/4 skin disorders was 2% in both the
727 ELOXATIN plus infusional 5-FU/LV and the infusional 5-FU/LV alone arms in the adjuvant
728 colon cancer patients. The incidence of hand-foot syndrome in patients previously untreated for
729 advanced colorectal cancer was 2% in the irinotecan plus 5-FU/LV arm and 7% in the
730 ELOXATIN and 5-FU/LV combination arm. The incidence of hand-foot syndrome in previously
731 treated patients was 13% in the 5-FU/LV arm and 11% in the ELOXATIN and 5-FU/LV
732 combination arm.

733 **Care of Intravenous Site:**

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

737

738 **Neurologic**

739 Peripheral sensory neuropathy was reported in adjuvant patients treated with the ELOXATIN
740 combination with a frequency of 92% (all grades) and 13% (grade 3), and by 18 months of follow
741 up, 21% patients had persistent peripheral sensory neuropathy (all grades). In these patients the
742 median cycle of onset for grade 3 peripheral sensory neuropathy was 9. In patients previously
743 untreated for advanced colorectal cancer neuropathy was reported in 82% (all grades) and 19%
744 (grade 3/4), and in the previously treated patients in 74% (all grades) and 7% (grade 3/4) events.
745 ELOXATIN is consistently associated with two types of peripheral neuropathy (see
746 PRECAUTIONS, Neuropathy). In the previously treated patients, the incidence of overall and
747 Grade 3/4 persistent peripheral neuropathy was 48% and 6%, respectively. The majority of the
748 patients (80%) that developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2
749 events. The median number of cycles administered on the ELOXATIN with 5-FU/LV
750 combination arm in the previously treated patients was 6.

751

752 **Pulmonary**

753 ELOXATIN has been associated with pulmonary fibrosis (see PRECAUTIONS, Pulmonary
754 Toxicity). One patient treated with the ELOXATIN combination regimen in the adjuvant trial
755 died from eosinophilic pneumonia.

756

757 **Allergic Reactions**

758 Grade 3/4 hypersensitivity to ELOXATIN has been observed in 2-3% of colon cancer patients.
759 These allergic reactions which can be fatal, can occur at any cycle, and were similar in nature and
760 severity to those reported with other platinum-containing compounds, such as rash, urticaria,
761 erythema, pruritus, and, rarely, bronchospasm and hypotension. The symptoms associated with
762 hypersensitivity reactions reported in the previously untreated patients were urticaria, pruritus,
763 flushing of the face, diarrhea associated with oxaliplatin infusion, shortness of breath,
764 bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. These
765 reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy,
766 and may require discontinuation of therapy (see WARNINGS for anaphylactic/anaphylactoid
767 reactions).

768

769 **Anticoagulation and Hemorrhage**

770 There have been reports while on study and from post-marketing surveillance of prolonged
771 prothrombin time and INR occasionally associated with hemorrhage in patients who received
772 ELOXATIN plus 5-FU/LV while on anticoagulants. Patients receiving ELOXATIN plus 5-
773 FU/LV and requiring oral anticoagulants may require closer monitoring.

774

775 **Renal**

776 About 5-10% of patients in all groups had some degree of elevation of serum creatinine. The
777 incidence of Grade 3/4 elevations in serum creatinine in the ELOXATIN and 5-FU/LV
778 combination arm was 1% in the previously treated patients. Serum creatinine measurements
779 were not reported in the adjuvant trial.

780

781 **Hepatic**

782 Hepatotoxicity (defined as elevation of liver enzymes) appears to be related to ELOXATIN
783 combination therapy (see PRECAUTIONS). The following tables list the clinical chemistry
784 changes associated with hepatic toxicity occurring in ≥5% of patients, based on adverse events
785 reported and NCI CTC grade for adjuvant patients and patients previously untreated for advanced
786 colorectal cancer, laboratory values and NCI CTC grade for previously treated patients.
787

788 **Table 22 - Adverse Hepatic Experiences in Patients with Stage II or III Colon**
789 **Cancer Receiving Adjuvant Therapy**

790 **(≥5% of patients)**

791

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

792

793

794 **Table 23 – Adverse Hepatic – Clinical Chemistry Experience in Patients Previously**
795 **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

796

797

798 **Table 24 – Adverse Hepatic – Clinical Chemistry Experience in Previously Treated**
799 **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

800

801 **Thromboembolism**

802 The incidence of thromboembolic events in adjuvant patients with colon cancer was 6% (1.8%
803 grade 3/4) in the infusional 5-FU/LV arm and 6% (1.2% grade 3/4) in the ELOXATIN and
804 infusional 5-FU/LV combined arm, respectively. The incidence was 6 and 9% of the patients
805 previously untreated for advanced colorectal cancer and previously treated patients in the
806 ELOXATIN and 5-FU/LV combination arm, respectively.

807

808 **Postmarketing Experience**

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

810 Body as a whole:

811 -angioedema, anaphylactic shock

812 Central and peripheral nervous system disorders:

813 -loss of deep tendon reflexes, dysarthria, Lhermitte's sign, cranial nerve palsies,
814 fasciculations

815 Liver and Gastrointestinal system disorders:

816 -severe diarrhea/vomiting resulting in hypokalemia, colitis (including clostridium difficile
817 diarrhea), metabolic acidosis; ileus; intestinal obstruction, pancreatitis; veno-occlusive
818 disease of liver also known as sinusoidal obstruction syndrome, and perisinusoidal
819 fibrosis which rarely may progress.

820 Hearing and vestibular system disorders:

821 -deafness

822 Platelet, bleeding, and clotting disorders:

823 -immuno-allergic thrombocytopenia

824 -prolongation of prothrombin time and of INR in patients receiving anticoagulants

825 Red Blood Cell disorders:

826 -hemolytic uremic syndrome, immuno-allergic hemolytic anemia

827 Respiratory system disorders:

828 -pulmonary fibrosis, and other interstitial lung diseases

829 Vision disorders:

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

831

832 **OVERDOSAGE**

833 There have been five ELOXATIN overdoses reported. One patient received two 130 mg/m²
834 doses of ELOXATIN (cumulative dose of 260 mg/m²) within a 24-hour period. The patient
835 experienced Grade 4 thrombocytopenia (<25,000/mm³) without any bleeding, which resolved.
836 Two other patients were mistakenly administered ELOXATIN instead of carboplatin. One
837 patient received a total ELOXATIN dose of 500 mg and the other received 650 mg. The first
838 patient experienced dyspnea, wheezing, paresthesia, profuse vomiting and chest pain on the day
839 of administration. She developed respiratory failure and severe bradycardia, and subsequently
840 did not respond to resuscitation efforts. The other patient also experienced dyspnea, wheezing,
841 paresthesia, and vomiting. Her symptoms resolved with supportive care. Another patient who
842 was mistakenly administered a 700 mg dose experienced rapid onset of dysesthesia. Inpatient
843 supportive care was given, including hydration, electrolyte support, and platelet transfusion.
844 Recovery occurred 15 days after the overdose. The last patient received an overdose of
845 oxaliplatin at 360 mg instead of 120 mg over a 1-hour infusion by mistake. At the end of the
846 infusion, the patient experienced 2 episodes of vomiting, laryngospasm, and paresthesia. The
847 patient fully recovered from the laryngospasm within half an hour. At the time of reporting, 1
848 hour after onset of the event, the patient was recovering from paresthesia. There is no known
849 antidote for ELOXATIN overdose. In addition to thrombocytopenia, the anticipated
850 complications of an ELOXATIN overdose include myelosuppression, nausea and vomiting,
851 diarrhea, and neurotoxicity. Patients suspected of receiving an overdose should be monitored,
852 and supportive treatment should be administered.

853

854 **DOSAGE AND ADMINISTRATION**

855

856 **Adjuvant Therapy in Patients with Stage III Colon Cancer**

857

858 Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6
859 months, i.e., 12 cycles, every 2 weeks, according to the dose schedule described below for
860 previously treated patients with advanced colorectal cancer.

861

862 **Therapy in Previously Untreated and Previously Treated Patients with Advanced**
863 **Colorectal Cancer**

864

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

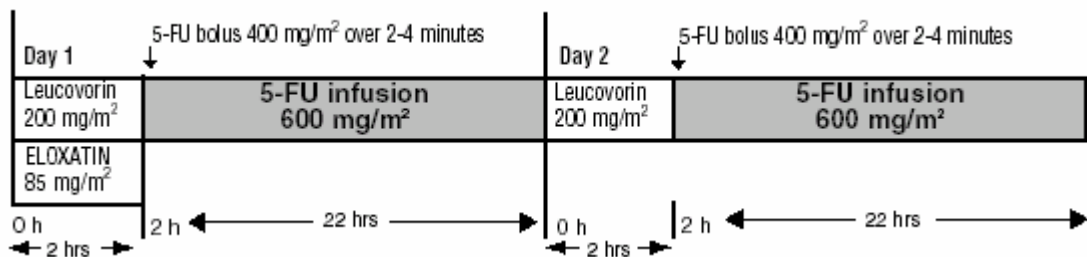
866 Day 1: ELOXATIN 85 mg/m² IV infusion in 250-500 mL D5W and leucovorin 200 mg/m² IV
867 infusion in D5W both given over 120 minutes at the same time in separate bags using a Y-line,
868 followed by 5-FU 400 mg/m² IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m² IV
869 infusion in 500 mL D5W (recommended) as a 22-hour continuous infusion.

870 Day 2: Leucovorin 200 mg/m² IV infusion over 120 minutes, followed by 5-FU 400 mg/m² IV
871 bolus given over 2-4 minutes, followed by 5-FU 600 mg/m² IV infusion in 500 mL D5W
872 (recommended) as a 22-hour continuous infusion.

873

874 **Figure 4**

875



876

877

878 Repeat cycle every 2 weeks.

879 The administration of ELOXATIN does not require prehydration.

880 Premedication with antiemetics, including 5-HT₃ blockers with or without dexamethasone, is
881 recommended.

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

883

884 **Dose Modification Recommendations**

885 Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and
886 laboratory tests (see Laboratory Tests). Prolongation of infusion time for ELOXATIN from 2
887 hours to 6 hours decreases the C_{max} by an estimated 32% and may mitigate acute toxicities. The
888 infusion times for 5-FU and leucovorin do not need to be changed.

889

890 **Adjuvant Therapy of Patients with Stage III Colon Cancer**

891

892 Neuropathy and other toxicities were graded using the NCI CTC scale version 1 (see
893 PRECAUTIONS, Neuropathy).

894

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

899

900 A dose reduction of ELOXATIN to 75 mg/m^2 and infusional 5-FU to 300 mg/m^2 bolus and 500
901 mg/m^2 22 hour infusion is recommended for patients after recovery from grade 3/4
902 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4
903 thrombocytopenia. The next dose should be delayed until: neutrophils $\geq 1.5 \times 10^9/\text{L}$ and platelets
904 $\geq 75 \times 10^9/\text{L}$.

905

906 **Dose Modifications in Therapy of Previously Untreated and Previously Treated**
907 **Patients with Advanced Colorectal Cancer**

908

909 Neuropathy was graded using a study-specific neurotoxicity scale (see PRECAUTIONS,
910 Neuropathy). Other toxicities were graded by the NCI CTC, Version 2.0.

911

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

916 A dose reduction of ELOXATIN to 65 mg/m^2 and 5-FU by 20% (300 mg/m^2 bolus and 500
917 mg/m^2 22-hour infusion) is recommended for patients after recovery from grade 3/4
918 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4
919 thrombocytopenia. The next dose should be delayed until: neutrophils $\geq 1.5 \times 10^9/\text{L}$ and platelets
920 $\geq 75 \times 10^9/\text{L}$.

921

922 **Preparation of Infusion Solution**

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

926 The lyophilized powder is reconstituted by adding 10 mL (for the 50 mg vial) or 20 mL (for the
927 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP. **Do not administer the**
928 **reconstituted solution without further dilution.** The reconstituted solution must be further
929 diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

930 After reconstitution in the original vial, the solution may be stored up to 24 hours under
931 refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of 5% Dextrose Injection,
932 USP, the shelf life is **6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours**
933 **under refrigeration [2-8°C (36-46°F)].**

934 ELOXATIN is not light sensitive.

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

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

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

944

945 **HOW SUPPLIED**

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

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

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

954

955 **Storage**

956 Store under normal lighting conditions at 25°C (77°F); excursions permitted to 15-30°C (59-
957 86°F) [see USP controlled room temperature].

958

959 **Handling and Disposal**

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

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

968

969 **REFERENCES**

970

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