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ELOXATIN™
(oxaliplatin for injection)

WARNING

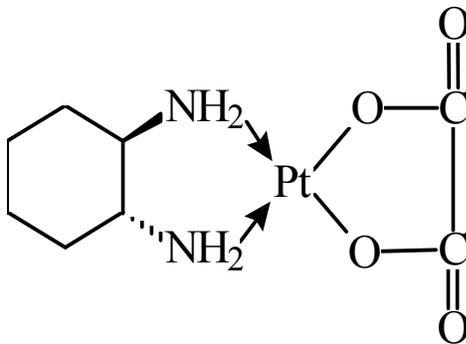
ELOXATIN (oxaliplatin for injection) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

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

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DESCRIPTION

8 ELOXATIN™ (oxaliplatin for injection) is an antineoplastic agent with the molecular formula
9 $C_8H_{14}N_2O_4Pt$ and the chemical name of *cis*-[(1*R*,2*R*)-1,2-cyclohexanediamine-*N,N'*]
10 [oxalato(2-)-*O,O'*] platinum. Oxaliplatin is an organoplatinum complex in which the
11 platinum atom is complexed with 1,2- diaminocyclohexane (DACH) and with an oxalate
12 ligand as a leaving group.



13
14
15 The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very
16 slightly soluble in methanol, and practically insoluble in ethanol and acetone.

17
18 ELOXATIN is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile,
19 preservative-free lyophilized powder for reconstitution. Lactose monohydrate is present as an
20 inactive ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths,
21 respectively.
22

23 **CLINICAL PHARMACOLOGY**

24

25 **Mechanism of Action**

26 Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives
27 via displacement of the labile oxalate ligand. Several transient reactive species are formed,
28 including monoquo and diaquo DACH platinum, which covalently bind with
29 macromolecules. Both inter- and intra-strand Pt-DNA cross-links are formed. Crosslinks are
30 formed between the *N*7 positions of two adjacent guanines (GG), adjacent adenine-guanines
31 (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit
32 DNA replication and transcription. Cytotoxicity is cell-cycle nonspecific.

33

34 **Pharmacology**

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

39

40 **Human Pharmacokinetics**

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

48

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

53

54 **Distribution**

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

62

63 **Metabolism**

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

66
67 Up to 17 platinum-containing derivatives have been observed in plasma ultrafiltrate samples
68 from patients, including several cytotoxic species (monochloro DACH platinum, dichloro
69 DACH platinum, and monoquo and diaquo DACH platinum) and a number of noncytotoxic,
70 conjugated species.

71
72 **Elimination**

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

80
81 **Pharmacokinetics in Special Populations**

82 **Renal Impairment**

83
84 The AUC_{0-48hr} of platinum in the plasma ultrafiltrate increases as renal function decreases.
85 The AUC_{0-48hr} of platinum in patients with mild (creatinine clearance, CL_{cr} 50 to 80 mL/min),
86 moderate (CL_{cr} 30 to <50 mL/min) and severe renal (CL_{cr} <30 mL/min) impairment is
87 increased by about 60, 140 and 190%, respectively, compared to patients with normal renal
88 function (CL_{cr} >80 mL/min)]. (See PRECAUTIONS and ADVERSE REACTIONS)

89
90 **Drug - Drug Interactions**

91 No pharmacokinetic interaction between 85 mg/m² of ELOXATIN and 5-FU has been observed
92 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.
97 No P450-mediated drug-drug interactions are therefore anticipated in patients.

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

102

103 **CLINICAL STUDIES**

104

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

107 A North American, multicenter, open-label, randomized controlled study was sponsored by
108 the National Cancer Institute (NCI) as an intergroup study led by the North Central Cancer
109 Treatment Group (NCCTG). The study had 7 arms at different times during its conduct, four
110 of which were closed due to either changes in the standard of care, toxicity, or simplification.
111 During the study, the control arm was changed to irinotecan plus 5-FU/LV. The results
112 reported below compared the efficacy and safety of two experimental regimens, ELOXATIN in
113 combination with infusional 5-FU/LV and a combination of ELOXATIN plus irinotecan, to an
114 approved control regimen of irinotecan plus 5-FU/LV in 795 concurrently randomized
115 patients previously untreated for locally advanced or metastatic colorectal cancer. After
116 completion of enrollment, the dose of irinotecan plus 5-FU/LV was decreased due to toxicity.
117 Patients had to be at least 18 years of age, have known locally advanced, locally recurrent, or
118 metastatic colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy
119 with curative intent, histologically proven colorectal adenocarcinoma, measurable or
120 evaluable disease, with an ECOG performance status 0,1, or 2. Patients had to have
121 granulocyte count $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, hemoglobin ≥ 9.0 gm/dL, creatinine
122 $\leq 1.5 \times$ ULN, total bilirubin ≤ 1.5 mg/dL, AST $\leq 5 \times$ ULN, and alkaline phosphatase $\leq 5 \times$
123 ULN. Patients may have received adjuvant therapy for resected Stage II or III disease
124 without recurrence within 12 months. The patients were stratified for ECOG performance
125 status (0, 1 vs. 2), prior adjuvant chemotherapy (yes vs. no), prior immunotherapy (yes vs.
126 no), and age (<65 vs. ≥ 65 years). Although no post study treatment was specified in the
127 protocol, 65 to 72% of patients received additional post study chemotherapy after study
128 treatment discontinuation on all arms. Fifty eight percent of patients on the ELOXATIN plus
129 5-FU/LV arm received an irinotecan-containing regimen and 23% of patients on the
130 irinotecan plus 5-FU/LV arm received oxaliplatin-containing regimens. Oxaliplatin was not
131 commercially available during the trial.

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

133

134 **Table 1 – Dosing Regimens in Patients Previously Untreated for Advanced Colorectal**
135 **Cancer Clinical Trial**

| Treatment Arm | Dose | Regimen |
|--|--|----------------|
| ELOXATIN + 5-FU/LV FOLFOX4 (N =267) | 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 |
| 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 |

136

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

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

141

| | 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 |

142

143 The length of a treatment cycle was 2 weeks for the ELOXATIN and 5-FU/LV regimen; 6
 144 weeks for the irinotecan plus 5-FU/LV regimen; and 3 weeks for the ELOXATIN plus
 145 irinotecan regimen. The median number of cycles administered per patient was 10 (23.9
 146 weeks) for the ELOXATIN and 5-FU/LV regimen, 4 (23.6 weeks) for the irinotecan plus 5-
 147 FU/LV regimen, and 7 (21.0 weeks) for the ELOXATIN plus irinotecan regimen.

148

149 Patients treated with the ELOXATIN and 5-FU/LV combination had a significantly longer time
 150 to tumor progression based on investigator assessment, longer overall survival, and a
 151 significantly higher confirmed response rate based on investigator assessment compared to
 152 patients given irinotecan plus 5-FU/LV. The following table summarizes the efficacy results.

153 **Table 3 – Summary of Efficacy**

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

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

155 **Based on all patients with measurable disease at baseline

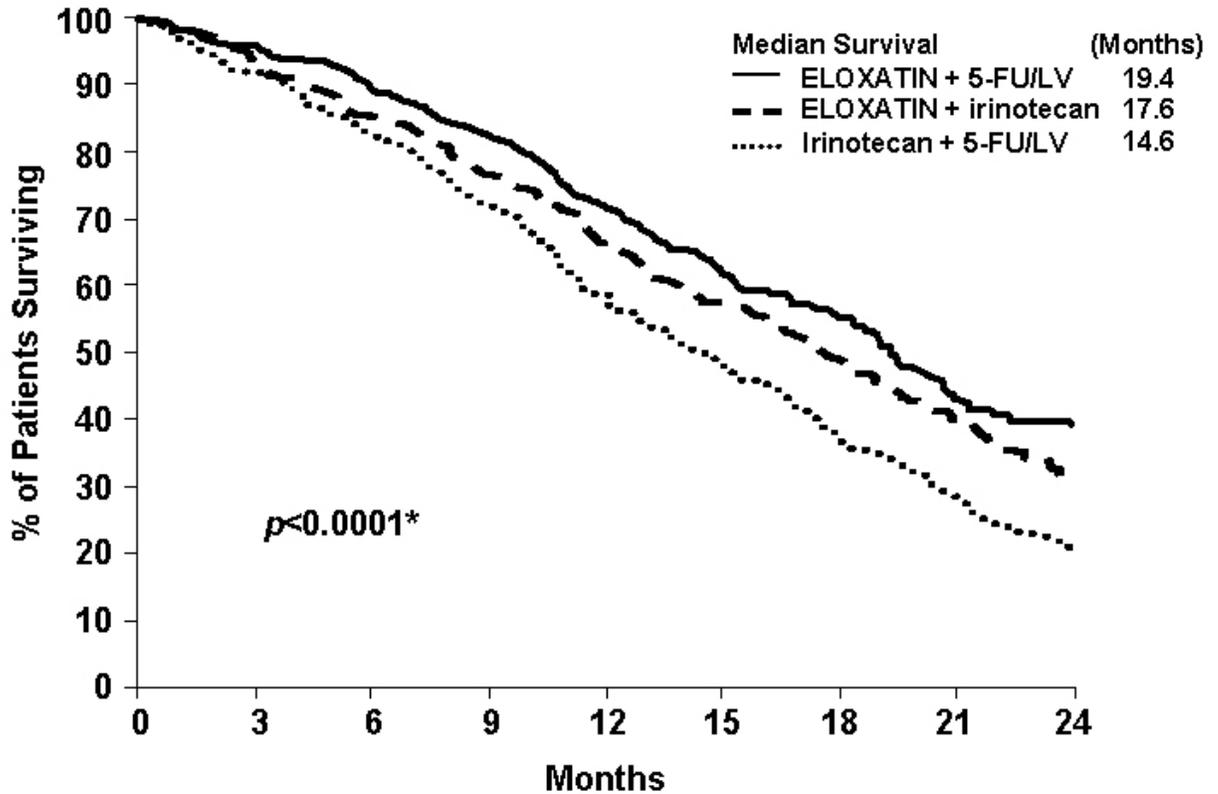
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157 The numbers in the response rate and TTP analysis are based on unblinded investigator
 158 assessment.

159

160

161 Figure 1 illustrates the Kaplan-Meier survival curves for the comparison of ELOXATIN and 5-
162 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.

163

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

170

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

173 A multicenter, open-label, randomized, three arm controlled study was conducted in the US
 174 and Canada comparing the efficacy and safety of ELOXATIN in combination with an infusional
 175 schedule of 5-FU/LV to the same dose and schedule of 5-FU/LV alone and to single agent
 176 oxaliplatin in patients with advanced colorectal cancer who had relapsed/progressed during or
 177 within 6 months of first line therapy with bolus 5-FU/LV and irinotecan. The study was
 178 intended to be analyzed for response rate after 450 patients were enrolled. Survival will be
 179 subsequently assessed in all patients enrolled in the completed study. Accrual to this study is
 180 complete, with 821 patients enrolled. Patients in the study had to be at least 18 years of age,
 181 have unresectable, measurable, histologically proven colorectal adenocarcinoma, with a
 182 Karnofsky performance status >50%. Patients had to have SGOT(AST) and SGPT(ALT) ≤ 2x
 183 the institution’s upper limit of normal (ULN), unless liver metastases were present and
 184 documented at baseline by CT or MRI scan, in which case ≤ 5x ULN was permitted. Patients
 185 had to have alkaline phosphatase ≤ 2x the institution’s ULN, unless liver metastases were
 186 present and documented at baseline by CT or MRI scan, in which cases ≤ 5x ULN was
 187 permitted. Prior radiotherapy was permitted if it had been completed at least 3 weeks before
 188 randomization.

189
 190 The dosing regimens of the three arms of the study are presented in the table below.
 191

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

| Treatment Arm | Dose | Regime n |
|-----------------------------|--|----------|
| ELOXATIN + 5-FU/LV (N =152) | 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 |
| 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 |

194

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

202
 203 The demographics of the patient population entered into this study are shown in the table
 204 below.

205
 206 **Table 5 – Patient Demographics in Refractory and Relapsed**
 207 **Colorectal Cancer Clinical Trial**

| | 5-FU/LV (N = 151) | ELOXATIN (N = 156) | ELOXATIN + 5-FU/LV (N = 152) |
|--------------------------------|-------------------------|-----------------------|------------------------------------|
| Sex: Male (%) | 54.3 | 60.9 | 57.2 |
| Female (%) | 45.7 | 39.1 | 42.8 |
| Median age (years) | 60.0 | 61.0 | 59.0 |
| Range | 21-80 | 27-79 | 22-88 |
| Race (%) | | | |
| Caucasian | 87.4 | 84.6 | 88.8 |
| Black | 7.9 | 7.1 | 5.9 |
| Asian | 1.3 | 2.6 | 2.6 |
| Other | 3.3 | 5.8 | 2.6 |
| KPS (%) | | | |
| 70 – 100 | 94.7 | 92.3 | 95.4 |
| 50 – 60 | 2.6 | 4.5 | 2.0 |
| Not reported | 2.6 | 3.2 | 2.6 |
| Prior radiotherapy (%) | 25.2 | 19.2 | 25.0 |
| Prior pelvic radiation (%) | 18.5 | 13.5 | 21.1 |
| Number of metastatic sites (%) | | | |
| 1 | 27.2 | 31.4 | 25.7 |
| ≥ 2 | 72.2 | 67.9 | 74.3 |
| Liver involvement (%) | | | |
| Liver only | 22.5 | 25.6 | 18.4 |
| Liver + other | 60.3 | 59.0 | 53.3 |

208
 209 The median number of cycles administered per patient was 6 for the ELOXATIN and 5-FU/LV
 210 combination and 3 each for 5-FU/LV alone and ELOXATIN alone.

211
 212 Patients treated with the combination of ELOXATIN and 5-FU/LV had an increased response
 213 rate compared to patients given 5-FU/LV or oxaliplatin alone. The efficacy results are
 214 summarized in the tables below.
 215

216
217

Table 6 - Response Rates (ITT Analysis)

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

218
219

Table 7 - Summary of Radiographic Time to Progression*

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

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*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.

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226
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228

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.

229
230
231
232

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.

233

INDICATIONS AND USAGE

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236

237

238

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

239

CONTRAINDICATIONS

240

241

242

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

243

244 **WARNINGS**

245

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

253

254 **Pregnancy Category D**

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

264

265 **PRECAUTIONS**

266

267 **General**

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

272 **Neuropathy**

273

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

276

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

279

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

292

293 An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% (grade 3/4) of patients
294 previously untreated for advanced colorectal cancer, and the previously treated patients is
295 characterized by subjective sensations of dysphagia or dyspnea, without any
296 laryngospasm or bronchospasm (no stridor or wheezing).

297

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

307

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

313

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

319

320 **Pulmonary Toxicity**

321

322 ELOXATIN has been associated with pulmonary fibrosis (<1% of study patients), which may be
323 fatal. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7%
324 (grade 3 and 4) in the ELOXATIN plus 5-FU/LV arm compared to 32% (any grade) and 5%
325 (grade 3 and 4) in the irinotecan plus 5-FU/LV arm of unknown duration for patients with
326 previously untreated colorectal cancer. In case of unexplained respiratory symptoms such as
327 non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, ELOXATIN
328 should be discontinued until further pulmonary investigation excludes interstitial lung disease
329 or pulmonary fibrosis.

330

331

332 **Information for Patients**

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

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

342

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

345

346 **Laboratory Tests**

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

350

351 **Laboratory Test Interactions**

352 None known.

353

354 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

360

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

371

372 **Pregnancy Category D - See WARNINGS**

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

378

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

381

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

390

391 **Geriatric Use** - No significant effect of age on the clearance of ultrafilterable platinum has
392 been observed. In the previously untreated for advanced colorectal cancer randomized
393 clinical trial (see **CLINICAL STUDIES**) of ELOXATIN, 160 patients treated with ELOXATIN
394 and 5-FU/LV were < 65 years and 99 patients were ≥ 65 years. The same efficacy
395 improvements in response rate, time to tumor progression, and overall survival were observed
396 in the ≥ 65 year old patients as in the overall study population. In the previously treated
397 randomized clinical trial (see **CLINICAL STUDIES**) of ELOXATIN, 95 patients treated with
398 ELOXATIN and 5-FU/LV were < 65 years and 55 patients were ≥ 65 years. The rates of overall
399 adverse events, including grade 3 and 4 events, were similar across and within arms in the
400 different age groups in both studies. The incidence of diarrhea, dehydration, hypokalemia,
401 leukopenia, fatigue and syncope were higher in patients ≥ 65 years old. No adjustment to
402 starting dose was required in patients ≥ 65 years old.

403

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

412

413 **ADVERSE REACTIONS**

414

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

419

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

421

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

426

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

430

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

436

437 The following table provides adverse events reported in the previously untreated for advanced
438 colorectal cancer study (see CLINICAL STUDIES) by body system and decreasing order of
439 frequency in the ELOXATIN and 5-FU/LV combination arm for events with overall incidences
440 $\geq 5\%$ and for grade 3/4 events with incidences $\geq 1\%$. This table does not include hematologic
441 and blood chemistry abnormalities; these are shown separately below.

442

443 **Table 8 – Adverse Experience Reported in Patients Previously Untreated for Advanced**
444 **Colorectal Cancer Clinical Trial**

445

($\geq 5\%$ of all patients and with $\geq 1\%$ NCI 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 (%) | Grade 3/4 (%) | All Grades (%) | Grade 3/4 (%) | All Grades (%) | Grade 3/4 (%) |
| Any Event | 99 | 82 | 98 | 70 | 99 | 76 |
| Allergy/Immunology | | | | | | |
| Hypersensitivity | 12 | 2 | 5 | 0 | 6 | 1 |
| Cardiovascular | | | | | | |
| Thrombosis | 6 | 5 | 6 | 6 | 3 | 3 |
| Hypotension | 5 | 3 | 6 | 3 | 4 | 3 |
| Constitutional Symptoms/Pain/Ocular/Visual | | | | | | |
| Fatigue | 70 | 7 | 58 | 11 | 66 | 16 |
| Abdominal Pain | 29 | 8 | 31 | 7 | 39 | 10 |
| Myalgia | 14 | 2 | 6 | 0 | 9 | 2 |
| Pain | 7 | 1 | 5 | 1 | 6 | 1 |
| Vision abnormal | 5 | 0 | 2 | 1 | 6 | 1 |
| Neuralgia | 5 | 0 | 0 | 0 | 2 | 1 |
| Dermatology/Skin | | | | | | |
| Skin reaction – hand/foot | 7 | 1 | 2 | 1 | 1 | 0 |
| Injection site reaction | 6 | 0 | 1 | 0 | 4 | 1 |
| Gastrointestinal | | | | | | |
| Nausea | 71 | 6 | 67 | 15 | 83 | 19 |
| Diarrhea | 56 | 12 | 65 | 29 | 76 | 25 |
| Vomiting | 41 | 4 | 43 | 13 | 64 | 23 |
| Stomatitis | 38 | 0 | 25 | 1 | 19 | 1 |
| Anorexia | 35 | 2 | 25 | 4 | 27 | 5 |
| Constipation | 32 | 4 | 27 | 2 | 21 | 2 |
| Diarrhea-colostomy | 13 | 2 | 16 | 7 | 16 | 3 |
| Gastrointestinal NOS | 5 | 2 | 4 | 2 | 3 | 2 |
| Hematology/Infection | | | | | | |
| Infection no ANC | 10 | 4 | 5 | 1 | 7 | 2 |
| Infection –ANC | 8 | 8 | 12 | 11 | 9 | 8 |
| Lymphopenia | 6 | 2 | 4 | 1 | 5 | 2 |
| Febrile neutropenia | 4 | 4 | 15 | 14 | 12 | 11 |
| Hepatic/Metabolic/Laboratory/Renal | | | | | | |
| Hyperglycemia | 14 | 2 | 11 | 3 | 12 | 3 |
| Hypokalemia | 11 | 3 | 7 | 4 | 6 | 2 |
| Dehydration | 9 | 5 | 16 | 11 | 14 | 7 |
| Hypoalbuminemia | 8 | 0 | 5 | 2 | 9 | 1 |
| Hyponatremia | 8 | 2 | 7 | 4 | 4 | 1 |
| Urinary frequency | 5 | 1 | 2 | 1 | 3 | 1 |
| Neurology | | | | | | |
| Overall Neuropathy | 82 | 19 | 18 | 2 | 69 | 7 |
| Paresthesias | 77 | 18 | 16 | 2 | 62 | 6 |
| Pharyngo-laryngeal dysesthesias | 38 | 2 | 1 | 0 | 28 | 1 |
| Neuro-sensory | 12 | 1 | 2 | 0 | 9 | 1 |
| Neuro NOS | 1 | 0 | 1 | 0 | 1 | 0 |
| Pulmonary | | | | | | |
| Cough | 35 | 1 | 25 | 2 | 17 | 1 |
| Dyspnea | 18 | 7 | 14 | 3 | 11 | 2 |
| Hiccups | 5 | 1 | 2 | 0 | 3 | 2 |

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

448 frequency in the ELOXATIN and 5-FU/LV combination arm for events with overall incidences
 449 $\geq 5\%$ but with incidences $< 1\%$ NCI Grade 3/4 events.

450

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

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

453

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

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

463 Four-hundred and fifty patients (about 150 receiving the combination of ELOXATIN and 5-
464 FU/LV) were studied in a randomized trial in patients with refractory and relapsed colorectal
465 cancer (See CLINICAL STUDIES). The adverse event profile in this study was similar to
466 that seen in other studies and the adverse reactions in this trial are shown in the tables below.
467

468
469
470 Thirteen per cent of patients in the ELOXATIN and 5-FU/LV-combination arm and 18% in the
471 5-FU/LV arm of the previously treated study had to discontinue treatment because of adverse
472 effects related to gastrointestinal, or hematologic adverse events, or neuropathies. Both 5-FU
473 and ELOXATIN are associated with gastrointestinal and hematologic adverse events. When
474 ELOXATIN is administered in combination with 5-FU, the incidence of these events is
475 increased.

476
477 The incidence of death within 30 days of treatment in the previously treated study, regardless
478 of causality, was 5% with the ELOXATIN and 5-FU/LV combination, 8% with ELOXATIN alone,
479 and 7% with 5-FU/LV. Of the 7 deaths that occurred on the ELOXATIN and 5-FU/LV
480 combination arm within 30 days of stopping treatment, 3 may have been treatment related,
481 associated with gastrointestinal bleeding or dehydration

482
483 The following table provides adverse events reported in the previously treated study (see
484 CLINICAL STUDIES) by body system and in decreasing order of frequency in the ELOXATIN
485 and 5-FU/LV combination arm for events with overall incidences ≥5% and for grade 3/4
486 events with incidences ≥ 1%. This table does not include hematologic and blood chemistry
487 abnormalities; these are shown separately below.

488
489
490
491

**Table 10 – Adverse Experience Reported In Previously Treated
Colorectal Cancer Clinical Trial
(≥5% of all patients and 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 (%) | 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 |

492
493
494
495
496

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

497
498
499
500

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

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

501

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

512

513 **Hematologic**

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

518

519 **Table 12 – Adverse Hematologic Experiences in Patients Previously Untreated for**
 520 **Advanced Colorectal Cancer**
 521 **(≥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 |

522

523 **Table 13 – Adverse Hematologic Experiences Previously Treated Patients**
 524 **(≥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 |

525

526 Thrombocytopenia

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

539

540 Neutropenia

541 Neutropenia was frequently observed with the combination of ELOXATIN and 5-FU/LV, with
542 Grade 3 and 4 events reported in 35% and 18% of the patients previously untreated for
543 advanced colorectal cancer, respectively. Grade 3 and 4 events were reported in 27% and
544 17% of previously treated patients, respectively. The incidence of febrile neutropenia in the
545 patients previously untreated for advanced colorectal cancer was 15% (3% of cycles) in the
546 irinotecan plus 5-FU/LV arm and 4% (less than 1% of cycles) in the ELOXATIN and 5-FU/LV
547 combination arm. Additionally, in this same population, infection with grade 3 or 4
548 neutropenia was 12% in the irinotecan plus 5-FU/LV, and 8% in the ELOXATIN and 5-FU/LV
549 combination. The incidence of febrile neutropenia in the previously treated patients was 1%
550 in the 5-FU/LV arm and 6% (less than 1% of cycles) in the ELOXATIN and 5-FU/LV
551 combination arm.

552

553 Gastrointestinal

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

560

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

567

568 **Dermatologic**

569 ELOXATIN did not increase the incidence of alopecia compared to 5-FU/LV alone. No
570 complete alopecia was reported. The incidence of hand-foot syndrome in patients previously
571 untreated for advanced colorectal cancer was 2% in the irinotecan plus 5-FU/LV arm and 7%
572 in the ELOXATIN and 5-FU/LV combination arm. The incidence of hand-foot syndrome in
573 previously treated patients was 13% in the 5-FU/LV arm and 11% in the ELOXATIN and 5-
574 FU/LV combination arm.

575

576 **Care of Intravenous Site:**

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

580

581 **Neurologic**

582 Overall, neuropathy was reported in patients previously untreated for advanced colorectal
583 cancer in 82% (all grades) and 19% (grade 3/4), and in the previously treated patients in 74%
584 (all grades) and 7% (grade 3/4) events. ELOXATIN is consistently associated with two types of
585 peripheral neuropathy (see **PRECAUTIONS, Neuropathy**). In the previously treated
586 patients, the incidence of overall and Grade 3/4 persistent peripheral neuropathy was 48% and
587 6%, respectively. The majority of the patients (80%) that developed grade 3 persistent
588 neuropathy progressed from prior Grade 1 or 2 events. The median number of cycles
589 administered on the ELOXATIN with 5-FU/LV combination arm in the previously treated
590 patients was 6.

591

592 **Pulmonary**

593

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

596

597 **Allergic reactions**

598 Hypersensitivity to ELOXATIN has been observed (<2% Grade 3/4) in clinical studies. These
599 allergic reactions which can be fatal, can occur at any cycle, and were similar in nature and
600 severity to those reported with other platinum-containing compounds such as, rash, urticaria,
601 erythema, pruritis, and, rarely, bronchospasm and hypotension. The symptoms associated
602 with hypersensitivity reactions reported in the previously untreated patients were urticaria,
603 pruritis, flushing of the face, diarrhea associated with oxaliplatin infusion, shortness of breath,
604 bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. These
605 reactions are usually managed with standard epinephrine, corticosteroid, antihistamine
606 therapy, and may require discontinuation of therapy. (see **WARNINGS** for
607 anaphylactic/anaphylactoid reactions.)

608

609 **Anticoagulation and Hemorrhage**

610

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

615
 616

Renal

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

620
 621

Hepatic

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

626
 627
 628
 629
 630

Table 14 – Adverse Hepatic – Clinical Chemistry Experience in Patients Previously Untreated for Advanced Colorectal Cancer ($\geq 5\%$ 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 |

631
 632
 633
 634
 635

Table 15 – Adverse Hepatic – Clinical Chemistry Experience in Previously Treated Patients ($\geq 5\%$ 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 |

636

637 **Thromboembolism**

638

639 The incidence of thromboembolic events was 6 and 9% of the patients previously untreated
640 for advanced colorectal cancer and previously treated patients in the ELOXATIN and 5-FU/LV
641 combination arm, respectively.

642

643 **Postmarketing Experience**

644

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

646

647 Body as a whole:

648 -angioedema, anaphylactic shock

649

650 Central and peripheral nervous system disorders:

651 -loss of deep tendon reflexes, dysarthria, Lhermittes' sign, cranial nerve palsies,
652 fasciculations

653

654 Gastrointestinal system disorders:

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

657

658 Hearing and vestibular system disorders:

659 -deafness

660

661 Platelet, bleeding, and clotting disorders:

662 -immuno-allergic thrombocytopenia
663 -prolongation of prothrombin time and of INR in patients receiving anticoagulants

664

665 Red Blood Cell disorders

666 -hemolytic uremic syndrome

667

668 Respiratory system disorders:

669 -pulmonary fibrosis, and other interstitial lung diseases

670

671 Vision disorders:

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

673

674 **OVERDOSAGE**

675 There have been five ELOXATIN overdoses reported. One patient received two 130 mg/m²
676 doses of ELOXATIN (cumulative dose of 260 mg/m²) within a 24 hour period. The patient
677 experienced Grade 4 thrombocytopenia (<25,000/mm³) without any bleeding, which
678 resolved. Two other patients were mistakenly administered ELOXATIN instead of
679 carboplatin. One patient received a total ELOXATIN dose of 500 mg and the other received
680 650 mg. The first patient experienced dyspnea, wheezing, paresthesia, profuse vomiting
681 and chest pain on the day of administration. She developed respiratory failure and severe
682 bradycardia, and subsequently did not respond to resuscitation efforts. The other patient
683 also experienced dyspnea, wheezing, paresthesia, and vomiting. Her symptoms resolved
684 with supportive care. Another patient who was mistakenly administered a 700 mg dose
685 experienced rapid onset of dysesthesia. Inpatient supportive care was given, including
686 hydration, electrolyte support, and platelet transfusion. Recovery occurred 15 days after
687 the overdose. The last patient received an overdose of oxaliplatin at 360 mg instead of
688 120 mg over a 1-hour infusion by mistake. At the end of the infusion, the patient
689 experienced 2 episodes of vomiting, laryngospasm, and paresthesia. The patient fully
690 recovered from the laryngospasm within half an hour. At the time of reporting, 1 hour
691 after onset of the event, the patient was recovering from paresthesia. There is no known
692 antidote for ELOXATIN overdose. In addition to thrombocytopenia, the anticipated
693 complications of an ELOXATIN overdose include myelosuppression, nausea and vomiting,
694 diarrhea, and neurotoxicity. Patients suspected of receiving an overdose should be
695 monitored, and supportive treatment should be administered.

696

697 **DOSAGE AND ADMINISTRATION**

698

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

700

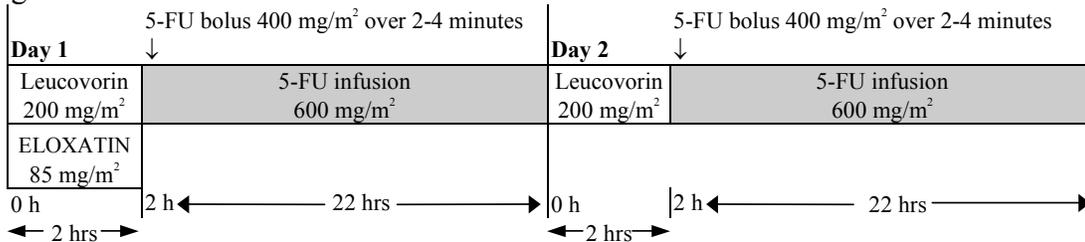
701 Day 1: ELOXATIN 85 mg/m² IV infusion in 250-500 mL D5W and leucovorin
 702 200 mg/m² IV infusion in D5W both given over 120 minutes at the same
 703 time in separate bags using a Y-line, followed by 5-FU 400 mg/m² IV
 704 bolus given over 2-4 minutes, followed by 5-FU 600 mg/m² IV infusion in
 705 500 mL D5W (recommended) as a 22-hour continuous infusion.

706

707 Day 2: Leucovorin 200 mg/m² IV infusion over 120 minutes, followed by 5-FU
 708 400 mg/m² IV bolus given over 2-4 minutes, followed by 5-FU 600 mg/m²
 709 IV infusion in 500 mL D5W (recommended) as a 22-hour continuous
 710 infusion.

711

712 Figure 2



713

714 Repeat cycle every 2 weeks.

715

716 The administration of ELOXATIN does not require prehydration.

717

718 Premedication with antiemetics, including 5-HT₃ blockers with or without dexamethasone, is
 719 recommended.

720

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

722

723 **Dose Modification Recommendations**

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

728

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

732

733 For patients who experience persistent Grade 2 neurosensory events that do not resolve, a
 734 dose reduction of ELOXATIN to 65 mg/m² should be considered. For patients with persistent

735 Grade 3 neurosensory events, discontinuing therapy should be considered. The 5-FU/LV
736 regimen need not be altered.

737

738 A dose reduction of ELOXATIN to 65 mg/m² and 5-FU by 20% (300 mg/m² bolus and 500
739 mg/m² 22 hour infusion) is recommended for patients after recovery from grade 3/4
740 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4
741 thrombocytopenia. The next dose should be delayed until: neutrophils $\geq 1.5 \times 10^9/L$, and
742 platelets $\geq 75 \times 10^9/L$.

743

744 **Preparation of Infusion Solution**

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

748

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

753

754 After reconstitution in the original vial, the solution may be stored up to 24 hours under
755 refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of
756 5% Dextrose Injection, USP, the shelf life is **6 hours at room temperature [20-25°C (68-**
757 **77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].** ELOXATIN is not light
758 sensitive.

759

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

764

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

767

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

771

772 **HOW SUPPLIED**

773

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

778

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

781

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

784

785 **Storage**

786 Store under normal lighting conditions at 25°C (77°F); excursions permitted to 15-30°C
787 (59-86°F) [see USP controlled room temperature].

788

789 **Handling and Disposal**

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

795

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

799

800 **REFERENCES**

801

- 802 1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and
803 Recommendations for Practice. Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.
- 804 2. Recommendations for the safe handling of parenteral antineoplastic drugs. NIH
805 Publication No. 83-2621. For sale by the Superintendent of Documents, U.S.
806 Government Printing Office, Washington, D.C. 20402.
- 807 3. AMA Council Report. Guidelines for handling parenteral antineoplastics. *JAMA*
808 1985;253(11):1590-1592.
- 809 4. National Study Commission on Cytotoxic Exposure. Recommendations for handling
810 cytotoxic agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National
811 Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and
812 Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
- 813 5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe
814 handling of antineoplastic agents. *Med J Australia* 1983;1:426-428.
- 815 6. Jones RB, et al. Safe handling of chemotherapeutic agents: a report from the Mount Sinai
816 Medical Center. *Ca - A Cancer Journal for Clinicians*. Sept./Oct. 1983:258-263.
- 817 7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on
818 handling cytotoxic and hazardous drugs. *Am J Hosp Pharm* 1990;47:1033-1049.
- 819 8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice
820 Guidelines). *Am J Hosp Pharm* 1996;53:1669-1685.

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