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XELODA[®]

(capecitabine)

TABLETS

Rx only

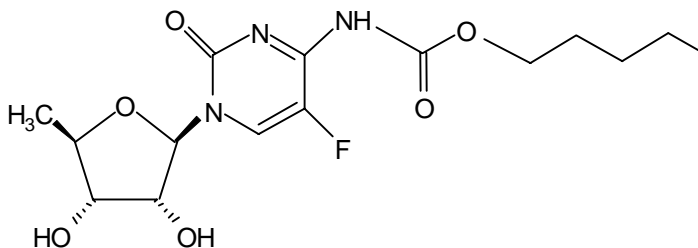
WARNING

XELODA Warfarin Interaction: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important XELODA-Warfarin drug interaction was demonstrated in a clinical pharmacology trial (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**). Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time XELODA was introduced. These events occurred within several days and up to several months after initiating XELODA therapy and, in a few cases, within 1 month after stopping XELODA. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

DESCRIPTION

XELODA (capecitabine) is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil.

The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and has a molecular weight of 359.35. Capecitabine has the following structural formula:



Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20°C.

XELODA is supplied as biconvex, oblong film-coated tablets for oral administration. Each light peach-colored tablet contains 150 mg capecitabine and each peach-colored

33 tablet contains 500 mg capecitabine. The inactive ingredients in XELODA include:
34 anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose,
35 microcrystalline cellulose, magnesium stearate and purified water. The peach or light
36 peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and
37 synthetic yellow and red iron oxides.

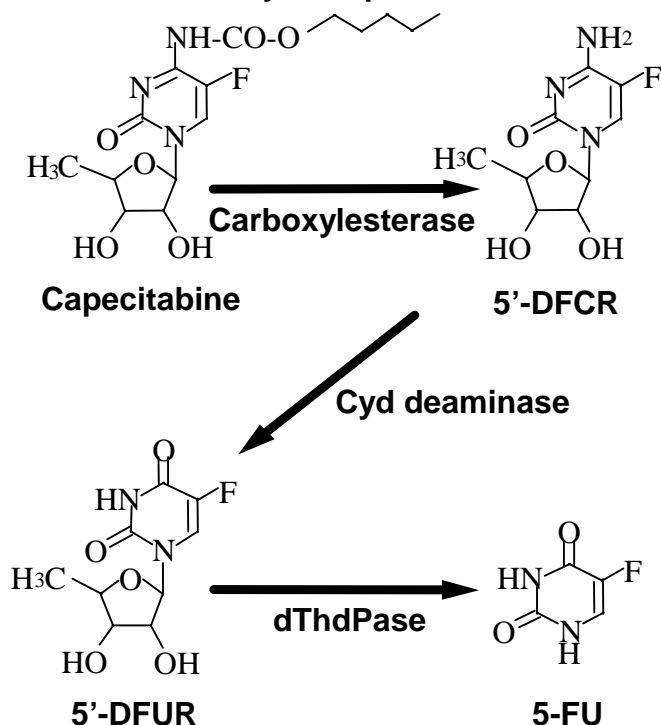
38 CLINICAL PHARMACOLOGY

39 XELODA is relatively non-cytotoxic in vitro. This drug is enzymatically converted to
40 5-fluorouracil (5-FU) in vivo.

41 Bioactivation

42 Capecitabine is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa
43 carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine
44 (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors,
45 subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). The enzyme,
46 thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU.
47 Many tissues throughout the body express thymidine phosphorylase. Some human
48 carcinomas express this enzyme in higher concentrations than surrounding normal
49 tissues.

50 Metabolic Pathway of capecitabine to 5-FU



51

52 Mechanism of Action

53 Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine
54 monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites
55 cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor,

56 N⁵⁻¹⁰-metylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently
57 bound ternary complex. This binding inhibits the formation of thymidylate from
58 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate,
59 which is essential for the synthesis of DNA, so that a deficiency of this compound can
60 inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate
61 FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This
62 metabolic error can interfere with RNA processing and protein synthesis.

63 **Pharmacokinetics in Colorectal Tumors and Adjacent Healthy Tissue**

64 Following oral administration of XELODA 7 days before surgery in patients with
65 colorectal cancer, the median ratio of 5-FU concentration in colorectal tumors to adjacent
66 tissues was 2.9 (range from 0.9 to 8.0). These ratios have not been evaluated in breast
67 cancer patients or compared to 5-FU infusion.

68 **Human Pharmacokinetics**

69 The pharmacokinetics of XELODA and its metabolites have been evaluated in about 200
70 cancer patients over a dosage range of 500 to 3500 mg/m²/day. Over this range, the
71 pharmacokinetics of XELODA and its metabolite, 5'-DFCR were dose proportional and
72 did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however,
73 were greater than proportional to the increase in dose and the AUC of 5-FU was 34%
74 higher on day 14 than on day 1. The elimination half-life of both parent capecitabine and
75 5-FU was about ¾ of an hour. The inter-patient variability in the C_{max} and AUC of 5-FU
76 was greater than 85%.

77 Following oral administration of 825 mg/m² capecitabine twice daily for 14 days,
78 Japanese patients (n=18) had about 36% lower C_{max} and 24% lower AUC for
79 capecitabine than the Caucasian patients (n=22). Japanese patients had also about 25%
80 lower C_{max} and 34% lower AUC for FBAL than the Caucasian patients. The clinical
81 significance of these differences is unknown. No significant differences occurred in the
82 exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU).

83 **Absorption, Distribution, Metabolism and Excretion**

84 Capecitabine reached peak blood levels in about 1.5 hours (T_{max}) with peak 5-FU levels
85 occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of
86 capecitabine with mean C_{max} and AUC_{0-∞} decreased by 60% and 35%, respectively. The
87 C_{max} and AUC_{0-∞} of 5-FU were also reduced by food by 43% and 21%, respectively.
88 Food delayed T_{max} of both parent and 5-FU by 1.5 hours (see **PRECAUTIONS** and
89 **DOSAGE AND ADMINISTRATION**).

90 Plasma protein binding of capecitabine and its metabolites is less than 60% and is not
91 concentration-dependent. Capecitabine was primarily bound to human albumin
92 (approximately 35%).

93 Capecitabine is extensively metabolized enzymatically to 5-FU. The enzyme
94 dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine
95 metabolism, to the much less toxic 5-fluoro-5, 6-dihydro-fluorouracil (FUH₂).
96 Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid

97 (FUPA). Finally, β -ureido-propionase cleaves FUPA to α -fluoro- β -alanine (FBAL)
98 which is cleared in the urine.

99 Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of
100 administered capecitabine dose is recovered in urine. Fecal excretion is minimal (2.6%).
101 The major metabolite excreted in urine is FBAL which represents 57% of the
102 administered dose. About 3% of the administered dose is excreted in urine as unchanged
103 drug.

104 A clinical phase 1 study evaluating the effect of XELODA on the pharmacokinetics of
105 docetaxel (Taxotere®) and the effect of docetaxel on the pharmacokinetics of XELODA
106 was conducted in 26 patients with solid tumors. XELODA was found to have no effect on
107 the pharmacokinetics of docetaxel (C_{\max} and AUC) and docetaxel has no effect on the
108 pharmacokinetics of capecitabine and the 5-FU precursor 5'-DFUR.

109 **Special Populations**

110 A population analysis of pooled data from the two large controlled studies in patients
111 with metastatic colorectal cancer (n=505) who were administered XELODA at
112 1250 mg/m² twice a day indicated that gender (202 females and 303 males) and race (455
113 white/Caucasian patients, 22 black patients, and 28 patients of other race) have no
114 influence on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL. Age has no significant
115 influence on the pharmacokinetics of 5'-DFUR and 5-FU over the range of 27 to 86
116 years. A 20% increase in age results in a 15% increase in AUC of FBAL (see
117 **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

118 **Hepatic Insufficiency**

119 XELODA has been evaluated in 13 patients with mild to moderate hepatic dysfunction
120 due to liver metastases defined by a composite score including bilirubin, AST/ALT and
121 alkaline phosphatase following a single 1255 mg/m² dose of XELODA. Both AUC_{0-∞} and
122 C_{max} of capecitabine increased by 60% in patients with hepatic dysfunction compared to
123 patients with normal hepatic function (n=14). The AUC_{0-∞} and C_{max} of 5-FU were not
124 affected. In patients with mild to moderate hepatic dysfunction due to liver metastases,
125 caution should be exercised when XELODA is administered. The effect of severe hepatic
126 dysfunction on XELODA is not known (see **PRECAUTIONS** and **DOSAGE AND**
127 **ADMINISTRATION**).

128 **Renal Insufficiency**

129 Following oral administration of 1250 mg/m² capecitabine twice a day to cancer patients
130 with varying degrees of renal impairment, patients with moderate (creatinine clearance =
131 30 to 50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment
132 showed 85% and 258% higher systemic exposure to FBAL on day 1 compared to normal
133 renal function patients (creatinine clearance >80 mL/min). Systemic exposure to
134 5'-DFUR was 42% and 71% greater in moderately and severely renal impaired patients,
135 respectively, than in normal patients. Systemic exposure to capecitabine was about 25%
136 greater in both moderately and severely renal impaired patients (see

137 **CONTRAINDICATIONS, WARNINGS, and DOSAGE AND**
138 **ADMINISTRATION).**

139 **Drug-Drug Interactions**

140 **Anticoagulants**

141 In four patients with cancer, chronic administration of capecitabine (1250 mg/m² bid)
142 with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and
143 decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients
144 increased by 2.8-fold, and the maximum observed mean INR value was increased by
145 91% (see **Boxed WARNING** and **PRECAUTIONS: Drug-Drug Interactions**).

146 **Drugs Metabolized by Cytochrome P450 Enzymes**

147 In vitro enzymatic studies with human liver microsomes indicated that capecitabine and
148 its metabolites (5'-DFUR, 5'-DFCR, 5-FU, and FBAL) had no inhibitory effects on
149 substrates of cytochrome P450 for the major isoenzymes such as 1A2, 2A6, 3A4, 2C9,
150 2C19, 2D6, and 2E1.

151 **Antacid**

152 When Maalox® (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing
153 antacid, was administered immediately after XELODA (1250 mg/m², n=12 cancer
154 patients), AUC and C_{max} increased by 16% and 35%, respectively, for capecitabine and
155 by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three
156 major metabolites (5'-DFUR, 5-FU, FBAL) of XELODA.

157 XELODA has a low potential for pharmacokinetic interactions related to plasma protein
158 binding.

159 **CLINICAL STUDIES**

160 **General**

161 The recommended dose of XELODA was determined in an open-label, randomized
162 clinical study, exploring the efficacy and safety of continuous therapy with capecitabine
163 (1331 mg/m²/day in two divided doses, n=39), intermittent therapy with capecitabine
164 (2510 mg/m²/day in two divided doses, n=34), and intermittent therapy with capecitabine
165 in combination with oral leucovorin (LV) (capecitabine 1657 mg/m²/day in two divided
166 doses, n=35; leucovorin 60 mg/day) in patients with advanced and/or metastatic
167 colorectal carcinoma in the first-line metastatic setting. There was no apparent advantage
168 in response rate to adding leucovorin to XELODA; however, toxicity was increased.
169 XELODA, 1250 mg/m² twice daily for 14 days followed by a 1-week rest, was selected
170 for further clinical development based on the overall safety and efficacy profile of the
171 three schedules studied.

172 **Adjuvant Colon Cancer**

173 A multicenter randomized, controlled phase 3 clinical trial in patients with Dukes' C
174 colon cancer provided data concerning the use of XELODA for the adjuvant treatment of

175 patients with colon cancer. The primary objective of the study was to compare disease-
 176 free survival (DFS) in patients receiving XELODA to those receiving IV 5-FU/LV alone.
 177 In this trial, 1987 patients were randomized either to treatment with XELODA
 178 1250 mg/m² orally twice daily for 2 weeks followed by a 1-week rest period, given as 3-
 179 week cycles for a total of 8 cycles (24 weeks) or IV bolus 5-FU 425 mg/m² and 20 mg/m²
 180 IV leucovorin on days 1 to 5, given as 4-week cycles for a total of 6 cycles (24 weeks).
 181 Patients in the study were required to be between 18 and 75 years of age with
 182 histologically-confirmed Dukes' stage C colon cancer with at least one positive lymph
 183 node and to have undergone (within 8 weeks prior to randomization) complete resection
 184 of the primary tumor without macroscopic or microscopic evidence of remaining tumor.
 185 Patients were also required to have no prior cytotoxic chemotherapy or immunotherapy
 186 (except steroids), and have an ECOG performance status of 0 or 1 (KPS ≥ 70%),
 187 ANC ≥ 1.5x10⁹/L, platelets ≥ 100 x 10⁹/L, serum creatinine ≤ 1.5 ULN, total
 188 bilirubin ≤ 1.5 ULN, AST/ALT ≤ 2.5 ULN and CEA within normal limits at time of
 189 randomization.

190 The baseline demographics for XELODA and 5-FU/LV patients are shown in **Table 1**.
 191 The baseline characteristics were well-balanced between arms.

192 **Table 1 Baseline Demographics**

	XELODA (n=1004)	5-FU/LV (n=983)
Age (median, years)	62	63
Range	(25-80)	(22-82)
Gender		
Male (n, %)	542 (54)	532 (54)
Female (n, %)	461 (46)	451 (46)
ECOG PS		
0 (n, %)	849 (85)	830 (85)
1 (n, %)	152 (15)	147 (15)
Staging – Primary Tumor		
PT1 (n, %)	12 (1)	6 (0.6)
PT2 (n, %)	90 (9)	92 (9)
PT3 (n, %)	763 (76)	746 (76)
PT4 (n, %)	138 (14)	139 (14)
Other (n, %)	1 (0.1)	0 (0)
Staging – Lymph Node		
pN1 (n, %)	695 (69)	694 (71)
pN2 (n, %)	305 (30)	288 (29)
Other (n, %)	4 (0.4)	1 (0.1)

193

194 All patients with normal renal function or mild renal impairment began treatment at the
 195 full starting dose of 1250 mg/m² orally twice daily. The starting dose was reduced in
 196 patients with moderate renal impairment (calculated creatinine clearance 30 to 50
 197 mL/min) at baseline (see **DOSAGE AND ADMINISTRATION**). Subsequently, for all

198 patients, doses were adjusted when needed according to toxicity. Dose management for
 199 XELODA included dose reductions, cycle delays and treatment interruptions (see
 200 **Table 2**).

201 **Table 2 Summary of Dose Modifications in X-ACT Study**

	XELODA N = 995	5-FU/LV N = 974
Median relative dose intensity (%)	93	92
Patients completing full course of treatment (%)	83	87
Patients with treatment interruption (%)	15	5
Patients with cycle delay (%)	46	29
Patients with dose reduction (%)	42	44
Patients with treatment interruption, cycle delay, or dose reduction (%)	57	52

202

203 The median follow-up at the time of the analysis was 53 months. The hazard ratio for
 204 DFS for XELODA compared to 5-FU/LV was 0.87 (95% C.I. 0.76 – 1.00). Because the
 205 upper 2-sided 95% confidence limit of hazard ratio was less than 1.20, XELODA was
 206 non-inferior to 5-FU/LV. The choice of the non-inferiority margin of 1.20 corresponds to
 207 the retention of approximately 75% of the 5-FU/LV effect on DFS.

208 Survival data were not mature at the time of the analysis with a median follow-up of 53
 209 months. The comparison of overall survival did not reach statistical significance for the
 210 test of difference (HR 0.88, 95% C.I. 0.74 – 1.05; p = 0.169).

211 **Table 3 Efficacy of XELODA vs 5-FU/LV in Adjuvant Treatment of**
 212 **Colon Cancer^a**

<i>All Randomized Population</i>	XELODA (n=1004)	5-FU/LV (n=983)
Median follow-up (months)	53	53
3-year Disease-free Survival Rates	66.0	62.9
Hazard Ratio (XELODA/5-FU/LV) (95% C.I. for Hazard Ratio), p-value ^b	0.87 (0.76 – 1.00) p = 0.055	

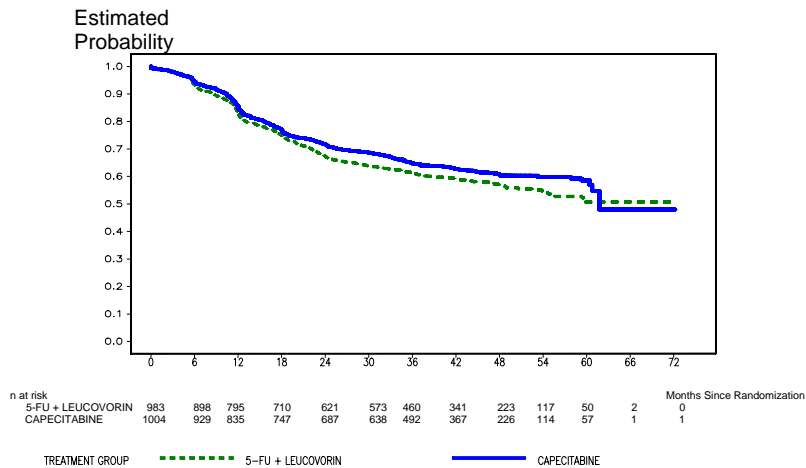
213 ^aApproximately 85% had 3-year DFS information

214 ^bLog-rank test for differences of XELODA vs 5-FU/LV

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216

217 **Figure 1** **Kaplan-Meier Estimates of Disease-Free Survival (All**
 218 **Randomized Population)^a**



^aXELODA has been demonstrated to be non-inferior to 5-FU/LV.

222 **Metastatic Colorectal Cancer**

223 Data from two open-label, multicenter, randomized, controlled clinical trials involving
 224 1207 patients support the use of XELODA in the first-line treatment of patients with
 225 metastatic colorectal carcinoma. The two clinical studies were identical in design and
 226 were conducted in 120 centers in different countries. Study 1 was conducted in the US,
 227 Canada, Mexico, and Brazil; Study 2 was conducted in Europe, Israel, Australia, New
 228 Zealand, and Taiwan. Altogether, in both trials, 603 patients were randomized to
 229 treatment with XELODA at a dose of 1250 mg/m² twice daily for 2 weeks followed by a
 230 1-week rest period and given as 3-week cycles; 604 patients were randomized to
 231 treatment with 5-FU and leucovorin (20 mg/m² leucovorin IV followed by 425 mg/m² IV
 232 bolus 5-FU, on days 1 to 5, every 28 days).

233 In both trials, overall survival, time to progression and response rate (complete plus
 234 partial responses) were assessed. Responses were defined by the World Health
 235 Organization criteria and submitted to a blinded independent review committee (IRC).
 236 Differences in assessments between the investigator and IRC were reconciled by the
 237 sponsor, blinded to treatment arm, according to a specified algorithm. Survival was
 238 assessed based on a non-inferiority analysis.

239 The baseline demographics for XELODA and 5-FU/LV patients are shown in **Table 4**.

240 **Table 4 Baseline Demographics of Controlled Colorectal Trials**

	Study 1		Study 2	
	XELODA (n=302)	5-FU/LV (n=303)	XELODA (n=301)	5-FU/LV (n=301)
Age (median, years)	64	63	64	64
Range	(23-86)	(24-87)	(29-84)	(36-86)
Gender				
Male (%)	181 (60)	197 (65)	172 (57)	173 (57)
Female (%)	121 (40)	106 (35)	129 (43)	128 (43)
Karnofsky PS (median)	90	90	90	90
Range	(70-100)	(70-100)	(70-100)	(70-100)
Colon (%)	222 (74)	232 (77)	199 (66)	196 (65)
Rectum (%)	79 (26)	70 (23)	101 (34)	105 (35)
Prior radiation therapy (%)	52 (17)	62 (21)	42 (14)	42 (14)
Prior adjuvant 5-FU (%)	84 (28)	110 (36)	56 (19)	41(14)

241

242 The efficacy endpoints for the two phase 3 trials are shown in **Table 5** and **Table 6**.

243 **Table 5 Efficacy of XELODA vs 5-FU/LV in Colorectal Cancer**
 244 **(Study 1)**

	XELODA (n=302)	5-FU/LV (n=303)
Overall Response Rate (%, 95% C.I.)	21 (16-26)	11 (8-15)
(<i>p</i> -value)	0.0014	
Time to Progression (Median, days, 95% C.I.)	128 (120-136)	131 (105-153)
Hazard Ratio (XELODA/5-FU/LV) 95% C.I. for Hazard Ratio	0.99 (0.84-1.17)	
Survival (Median, days, 95% C.I.)	380 (321-434)	407 (366-446)
Hazard Ratio (XELODA/5-FU/LV) 95% C.I. for Hazard Ratio	1.00 0.84-1.18	

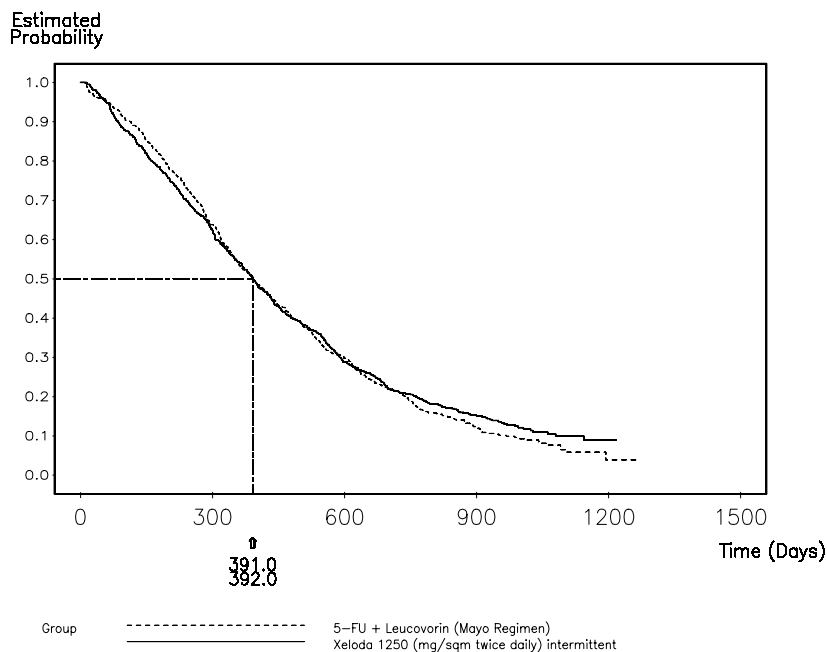
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246 **Table 6 Efficacy of XELODA vs 5-FU/LV in Colorectal Cancer**
 247 **(Study 2)**

	XELODA (n=301)	5-FU/LV (n=301)
Overall Response Rate (%, 95% C.I.)	21 (16-26)	14 (10-18)
(<i>p</i> -value)	0.027	
Time to Progression (Median, days, 95% C.I.)	137 (128-165)	131 (102-156)
Hazard Ratio (XELODA/5-FU/LV)	0.97	
95% C.I. for Hazard Ratio	0.82-1.14	
Survival (Median, days, 95% C.I.)	404 (367-452)	369 (338-430)
Hazard Ratio (XELODA/5-FU/LV)	0.92	
95% C.I. for Hazard Ratio	0.78-1.09	

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249 **Figure 2 Kaplan-Meier Curve for Overall Survival of Pooled Data**
 250 **(Studies 1 and 2)**



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252 XELODA was superior to 5-FU/LV for objective response rate in Study 1 and Study 2.
 253 The similarity of XELODA and 5-FU/LV in these studies was assessed by examining the
 254 potential difference between the two treatments. In order to assure that XELODA has a
 255 clinically meaningful survival effect, statistical analyses were performed to determine the
 256 percent of the survival effect of 5-FU/LV that was retained by XELODA. The estimate of
 257 the survival effect of 5-FU/LV was derived from a meta-analysis of ten randomized

258 studies from the published literature comparing 5-FU to regimens of 5-FU/LV that were
259 similar to the control arms used in these Studies 1 and 2. The method for comparing the
260 treatments was to examine the worst case (95% confidence upper bound) for the
261 difference between 5-FU/LV and XELODA, and to show that loss of more than 50% of
262 the 5-FU/LV survival effect was ruled out. It was demonstrated that the percent of the
263 survival effect of 5-FU/LV maintained was at least 61% for Study 2 and 10% for Study 1.
264 The pooled result is consistent with a retention of at least 50% of the effect of 5-FU/LV.
265 It should be noted that these values for preserved effect are based on the upper bound of
266 the 5-FU/LV vs XELODA difference. These results do not exclude the possibility of true
267 equivalence of XELODA to 5-FU/LV (see **Table 5**, **Table 6**, and **Figure 2**).

268 **Breast Cancer**

269 XELODA has been evaluated in clinical trials in combination with docetaxel
270 (Taxotere®) and as monotherapy.

271 **Breast Cancer Combination Therapy**

272 The dose of XELODA used in the phase 3 clinical trial in combination with docetaxel
273 was based on the results of a phase 1 study, where a range of doses of docetaxel
274 administered in 3-week cycles in combination with an intermittent regimen of XELODA
275 (14 days of treatment, followed by a 7-day rest period) were evaluated. The combination
276 dose regimen was selected based on the tolerability profile of the 75 mg/m² administered
277 in 3-week cycles of docetaxel in combination with 1250 mg/m² twice daily for 14 days of
278 XELODA administered in 3-week cycles. The approved dose of 100 mg/m² of docetaxel
279 administered in 3-week cycles was the control arm of the phase 3 study.

280 XELODA in combination with docetaxel was assessed in an open-label, multicenter,
281 randomized trial in 75 centers in Europe, North America, South America, Asia, and
282 Australia. A total of 511 patients with metastatic breast cancer resistant to, or recurring
283 during or after an anthracycline-containing therapy, or relapsing during or recurring
284 within 2 years of completing an anthracycline-containing adjuvant therapy were enrolled.
285 Two hundred and fifty-five (255) patients were randomized to receive XELODA
286 1250 mg/m² twice daily for 14 days followed by 1 week without treatment and docetaxel
287 75 mg/m² as a 1-hour intravenous infusion administered in 3-week cycles. In the
288 monotherapy arm, 256 patients received docetaxel 100 mg/m² as a 1-hour intravenous
289 infusion administered in 3-week cycles. Patient demographics are provided in **Table 7**.

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**Table 7 Baseline Demographics and Clinical Characteristics
XELODA and Docetaxel Combination vs Docetaxel in Breast
Cancer Trial**

	XELODA + Docetaxel (n=255)	Docetaxel (n=256)
<i>Age</i> (median, years)	52	51
<i>Karnofsky PS</i> (median)	90	90
<i>Site of Disease</i>		
Lymph nodes	121 (47%)	125 (49%)
Liver	116 (45%)	122 (48%)
Bone	107 (42%)	119 (46%)
Lung	95 (37%)	99 (39%)
Skin	73 (29%)	73 (29%)
<i>Prior Chemotherapy</i>		
Anthracycline ¹	255 (100%)	256 (100%)
5-FU	196 (77%)	189 (74%)
Paclitaxel	25 (10%)	22 (9%)
<i>Resistance to an Anthracycline</i>		
No resistance	19 (7%)	19 (7%)
Progression on anthracycline therapy	65 (26%)	73 (29%)
Stable disease after 4 cycles of anthracycline therapy	41 (16%)	40 (16%)
Relapsed within 2 years of completion of anthracycline-adjuvant therapy	78 (31%)	74 (29%)
Experienced a brief response to anthracycline therapy, with subsequent progression while on therapy or within 12 months after last dose	51 (20%)	50 (20%)
<i>No. of Prior Chemotherapy Regimens for Treatment of Metastatic Disease</i>		
0	89 (35%)	80 (31%)
1	123 (48%)	135 (53%)
2	43 (17%)	39 (15%)
3	0 (0%)	2 (1%)

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¹Includes 10 patients in combination and 18 patients in monotherapy arms treated with an anthracenedione
XELODA in combination with docetaxel resulted in statistically significant improvement in time to disease progression, overall survival and objective response rate compared to monotherapy with docetaxel as shown in **Table 8, Figure 3, and Figure 4.**

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Table 8 Efficacy of XELODA and Docetaxel Combination vs Docetaxel Monotherapy

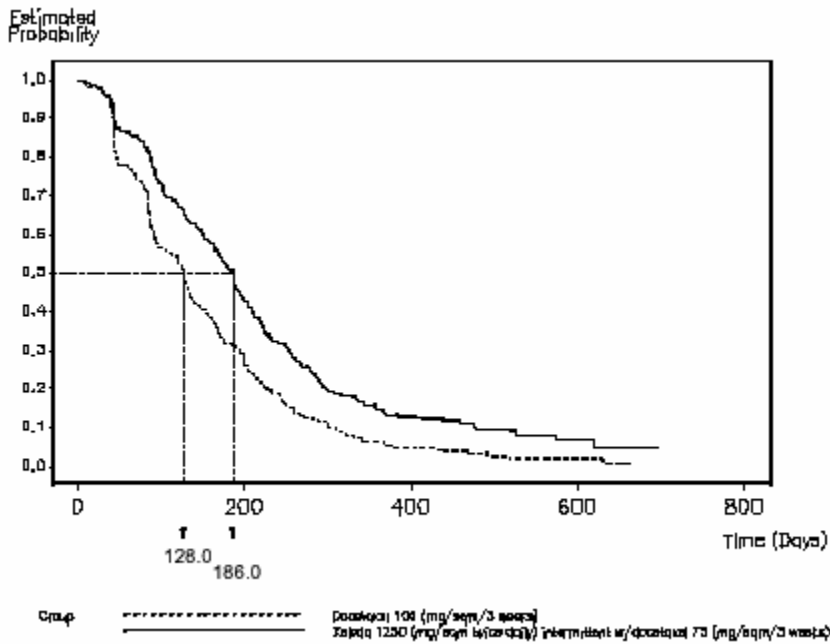
Efficacy Parameter	Combination Therapy	Monotherapy	p-value	Hazard Ratio
Time to Disease Progression				
Median Days	186	128	0.0001	0.643
95% C.I.	(165-198)	(105-136)		
Overall Survival				
Median Days	442	352	0.0126	0.775
95% C.I.	(375-497)	(298-387)		
Response Rate¹	32%	22%	0.009	NA ²

300 ¹ The response rate reported represents a reconciliation of the investigator and IRC assessments performed
301 by the sponsor according to a predefined algorithm.

302 ² NA = Not Applicable

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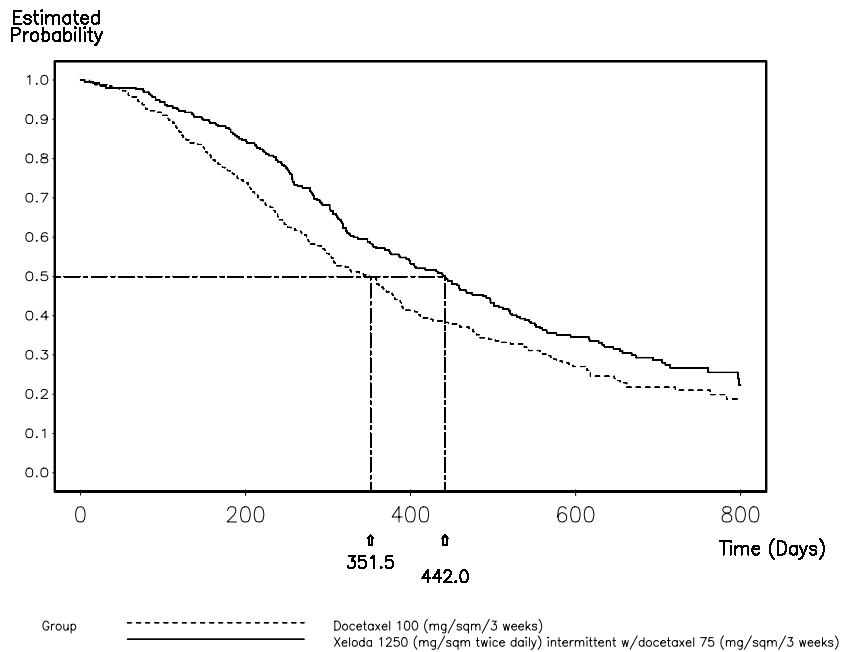
304 **Figure 3 Kaplan-Meier Estimates for Time to Disease Progression**
305 **XELODA and Docetaxel vs Docetaxel**



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Figure 4 Kaplan-Meier Estimates of Survival
XELODA and Docetaxel vs Docetaxel



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310 Breast Cancer Monotherapy

311 The antitumor activity of XELODA as a monotherapy was evaluated in an open-label
312 single-arm trial conducted in 24 centers in the US and Canada. A total of 162 patients
313 with stage IV breast cancer were enrolled. The primary endpoint was tumor response rate
314 in patients with measurable disease, with response defined as a $\geq 50\%$ decrease in sum of
315 the products of the perpendicular diameters of bidimensionally measurable disease for at
316 least 1 month. XELODA was administered at a dose of 1255 mg/m^2 twice daily for 2
317 weeks followed by a 1-week rest period and given as 3-week cycles. The baseline
318 demographics and clinical characteristics for all patients ($n=162$) and those with
319 measurable disease ($n=135$) are shown in **Table 9**. Resistance was defined as progressive
320 disease while on treatment, with or without an initial response, or relapse within 6 months
321 of completing treatment with an anthracycline-containing adjuvant chemotherapy
322 regimen.

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**Table 9 Baseline Demographics and Clinical Characteristics
Single Arm Breast Cancer Trial**

	Patients With Measurable Disease (n=135)	All Patients (n=162)
<i>Age</i> (median, years)	55	56
<i>Karnofsky PS</i>	90	90
No. Disease Sites		
1-2	43 (32%)	60 (37%)
3-4	63 (46%)	69 (43%)
>5	29 (22%)	34 (21%)
Dominant Site of Disease		
Visceral ¹	101 (75%)	110 (68%)
Soft Tissue	30 (22%)	35 (22%)
Bone	4 (3%)	17 (10%)
Prior Chemotherapy		
Paclitaxel	135 (100%)	162 (100%)
Anthracycline ²	122 (90%)	147 (91%)
5-FU	110 (81%)	133 (82%)
Resistance to Paclitaxel	103 (76%)	124 (77%)
Resistance to an Anthracycline ²	55 (41%)	67 (41%)
Resistance to both Paclitaxel and an Anthracycline ²	43 (32%)	51 (31%)

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¹Lung, pleura, liver, peritoneum

²Includes 2 patients treated with an anthracenedione

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Antitumor responses for patients with disease resistant to both paclitaxel and an anthracycline are shown in **Table 10**.

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**Table 10 Response Rates in Doubly-Resistant Patients
Single-Arm Breast Cancer Trial**

	Resistance to Both Paclitaxel and an Anthracycline (n=43)
CR	0
PR ¹	11
CR + PR ¹	11
Response Rate ¹ (95% C.I.)	25.6% (13.5, 41.2)
Duration of Response, ¹ Median in days ² (Range)	154 (63 - 233)

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333

¹Includes 2 patients treated with an anthracenedione

²From date of first response

334

335 For the subgroup of 43 patients who were doubly resistant, the median time to
336 progression was 102 days and the median survival was 255 days. The objective response
337 rate in this population was supported by a response rate of 18.5% (1 CR, 24 PRs) in the
338 overall population of 135 patients with measurable disease, who were less resistant to
339 chemotherapy (see **Table 9**). The median time to progression was 90 days and the
340 median survival was 306 days.

341 **INDICATIONS AND USAGE**

342 **Colorectal Cancer**

- 343 • XELODA is indicated as a single agent for adjuvant treatment in patients with
344 Dukes' C colon cancer who have undergone complete resection of the primary
345 tumor when treatment with fluoropyrimidine therapy alone is preferred.
346 XELODA was non-inferior to 5-fluorouracil and leucovorin (5-FU/LV) for
347 disease-free survival (DFS). Although neither XELODA nor combination
348 chemotherapy prolongs overall survival (OS), combination chemotherapy has
349 been demonstrated to improve disease-free survival compared to 5-FU/LV.
350 Physicians should consider these results when prescribing single-agent XELODA
351 in the adjuvant treatment of Dukes' C colon cancer.
- 352 • XELODA is indicated as first-line treatment of patients with metastatic colorectal
353 carcinoma when treatment with fluoropyrimidine therapy alone is preferred.
354 Combination chemotherapy has shown a survival benefit compared to 5-FU/LV
355 alone. A survival benefit over 5-FU/LV has not been demonstrated with
356 XELODA monotherapy. Use of XELODA instead of 5-FU/LV in combinations
357 has not been adequately studied to assure safety or preservation of the survival
358 advantage.

359 **Breast Cancer**

- 360 • XELODA in combination with docetaxel is indicated for the treatment of patients
361 with metastatic breast cancer after failure of prior anthracycline-containing
362 chemotherapy.
- 363 • XELODA monotherapy is also indicated for the treatment of patients with
364 metastatic breast cancer resistant to both paclitaxel and an anthracycline-
365 containing chemotherapy regimen or resistant to paclitaxel and for whom further
366 anthracycline therapy is not indicated, eg, patients who have received cumulative
367 doses of 400 mg/m² of doxorubicin or doxorubicin equivalents. Resistance is
368 defined as progressive disease while on treatment, with or without an initial
369 response, or relapse within 6 months of completing treatment with an
370 anthracycline-containing adjuvant regimen.

371 **CONTRAINDICATIONS**

372 XELODA is contraindicated in patients with known hypersensitivity to capecitabine or to
373 any of its components. XELODA is contraindicated in patients who have a known

374 hypersensitivity to 5-fluorouracil. XELODA is contraindicated in patients with known
375 dihydropyrimidine dehydrogenase (DPD) deficiency. XELODA is also contraindicated in
376 patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockcroft
377 and Gault]) (see **CLINICAL PHARMACOLOGY: Special Populations**).

378 **WARNINGS**

379 **Renal Insufficiency**

380 Patients with moderate renal impairment at baseline require dose reduction (see
381 **DOSAGE AND ADMINISTRATION**). Patients with mild and moderate renal
382 impairment at baseline should be carefully monitored for adverse events. Prompt
383 interruption of therapy with subsequent dose adjustments is recommended if a patient
384 develops a grade 2 to 4 adverse event as outlined in **Table 18** in **DOSAGE AND**
385 **ADMINISTRATION**.

386 **Coagulopathy**

387 See **Boxed WARNING**.

388 **Diarrhea**

389 XELODA can induce diarrhea, sometimes severe. Patients with severe diarrhea should be
390 carefully monitored and given fluid and electrolyte replacement if they become
391 dehydrated. In 875 patients with either metastatic breast or colorectal cancer who
392 received XELODA monotherapy, the median time to first occurrence of grade 2 to 4
393 diarrhea was 34 days (range from 1 to 369 days). The median duration of grade 3 to 4
394 diarrhea was 5 days. National Cancer Institute of Canada (NCIC) grade 2 diarrhea is
395 defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an
396 increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as
397 an increase of ≥ 10 stools/day or grossly bloody diarrhea or the need for parenteral
398 support. If grade 2, 3 or 4 diarrhea occurs, administration of XELODA should be
399 immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1.
400 Following a reoccurrence of grade 2 diarrhea or occurrence of any grade 3 or 4 diarrhea,
401 subsequent doses of XELODA should be decreased (see **DOSAGE AND**
402 **ADMINISTRATION**). Standard antidiarrheal treatments (eg, loperamide) are
403 recommended.

404 Necrotizing enterocolitis (typhlitis) has been reported.

405 **Geriatric Patients**

406 Patients ≥ 80 years old may experience a greater incidence of grade 3 or 4 adverse events
407 (see **PRECAUTIONS: Geriatric Use**). In 875 patients with either metastatic breast or
408 colorectal cancer who received XELODA monotherapy, 62% of the 21 patients ≥ 80 years
409 of age treated with XELODA experienced a treatment-related grade 3 or 4 adverse event:
410 diarrhea in 6 (28.6%), nausea in 3 (14.3%), hand-and-foot syndrome in 3 (14.3%), and
411 vomiting in 2 (9.5%) patients. Among the 10 patients 70 years of age and greater (no
412 patients were >80 years of age) treated with XELODA in combination with docetaxel,

413 30% (3 out of 10) of patients experienced grade 3 or 4 diarrhea and stomatitis, and 40%
414 (4 out of 10) experienced grade 3 hand-and-foot syndrome.

415 Among the 67 patients ≥ 60 years of age receiving XELODA in combination with
416 docetaxel, the incidence of grade 3 or 4 treatment-related adverse events, treatment-
417 related serious adverse events, withdrawals due to adverse events, treatment
418 discontinuations due to adverse events and treatment discontinuations within the first two
419 treatment cycles was higher than in the < 60 years of age patient group.

420 In 995 patients receiving XELODA as adjuvant therapy for Dukes' C colon cancer after
421 resection of the primary tumor, 41% of the 398 patients ≥ 65 years of age treated with
422 XELODA experienced a treatment-related grade 3 or 4 adverse event: hand-and-foot
423 syndrome in 75 (18.8%), diarrhea in 52 (13.1%), stomatitis in 12 (3.0%),
424 neutropenia/granulocytopenia in 11 (2.8%), vomiting in 6 (1.5%), and nausea in 5 (1.3%)
425 patients. In patients ≥ 65 years of age (all randomized population; capecitabine 188
426 patients, 5-FU/LV 208 patients) treated for Dukes' C colon cancer after resection of the
427 primary tumor, the hazard ratios for disease-free survival and overall survival for
428 XELODA compared to 5-FU/LV were 1.01 (95% C.I. 0.80 – 1.27) and 1.04 (95% C.I.
429 0.79 – 1.37), respectively.

430 **Pregnancy**

431 XELODA may cause fetal harm when given to a pregnant woman. Capecitabine at doses
432 of 198 mg/kg/day during organogenesis caused malformations and embryo death in mice.
433 In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values
434 about 0.2 times the corresponding values in patients administered the recommended daily
435 dose. Malformations in mice included cleft palate, anophthalmia, microphthalmia,
436 oligodactyly, polydactyly, syndactyly, kinky tail and dilation of cerebral ventricles. At
437 doses of 90 mg/kg/day, capecitabine given to pregnant monkeys during organogenesis
438 caused fetal death. This dose produced 5'-DFUR AUC values about 0.6 times the
439 corresponding values in patients administered the recommended daily dose. There are no
440 adequate and well-controlled studies in pregnant women using XELODA. If the drug is
441 used during pregnancy, or if the patient becomes pregnant while receiving this drug, the
442 patient should be apprised of the potential hazard to the fetus. Women of childbearing
443 potential should be advised to avoid becoming pregnant while receiving treatment with
444 XELODA.

445 **PRECAUTIONS**

446 **General**

447 Patients receiving therapy with XELODA should be monitored by a physician
448 experienced in the use of cancer chemotherapeutic agents. Most adverse events are
449 reversible and do not need to result in discontinuation, although doses may need to be
450 withheld or reduced (see **DOSAGE AND ADMINISTRATION**).

451 **Combination With Other Drugs**

452 Use of XELODA in combination with irinotecan has not been adequately studied.

453 Hand-and-Foot Syndrome

454 Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced
455 acral erythema) is a cutaneous toxicity. Median time to onset was 79 days (range from 11
456 to 360 days) with a severity range of grades 1 to 3 for patients receiving XELODA
457 monotherapy in the metastatic setting. Grade 1 is characterized by any of the following:
458 numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands
459 and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 hand-and-
460 foot syndrome is defined as painful erythema and swelling of the hands and/or feet and/or
461 discomfort affecting the patient's activities of daily living. Grade 3 hand-and-foot
462 syndrome is defined as moist desquamation, ulceration, blistering or severe pain of the
463 hands and/or feet and/or severe discomfort that causes the patient to be unable to work or
464 perform activities of daily living. If grade 2 or 3 hand-and-foot syndrome occurs,
465 administration of XELODA should be interrupted until the event resolves or decreases in
466 intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of
467 XELODA should be decreased (see **DOSAGE AND ADMINISTRATION**).

468 Cardiotoxicity

469 The cardiotoxicity observed with XELODA includes myocardial infarction/ischemia,
470 angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic
471 changes, and cardiomyopathy. These adverse events may be more common in patients
472 with a prior history of coronary artery disease.

473 Dihydropyrimidine Dehydrogenase Deficiency

474 Rarely, unexpected, severe toxicity (eg, stomatitis, diarrhea, neutropenia and
475 neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of
476 dihydropyrimidine dehydrogenase (DPD) activity. A link between decreased levels of
477 DPD and increased, potentially fatal toxic effects of 5-fluorouracil therefore cannot be
478 excluded.

479 Hepatic Insufficiency

480 Patients with mild to moderate hepatic dysfunction due to liver metastases should be
481 carefully monitored when XELODA is administered. The effect of severe hepatic
482 dysfunction on the disposition of XELODA is not known (see **CLINICAL**
483 **PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

484 Hyperbilirubinemia

485 In 875 patients with either metastatic breast or colorectal cancer who received at least one
486 dose of XELODA 1250 mg/m² twice daily as monotherapy for 2 weeks followed by a
487 1-week rest period, grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133)
488 of patients and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 3.9% (n=34) of
489 patients. Of 566 patients who had hepatic metastases at baseline and 309 patients without
490 hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 22.8% and
491 12.3%, respectively. Of the 167 patients with grade 3 or 4 hyperbilirubinemia, 18.6%
492 (n=31) also had postbaseline elevations (grades 1 to 4, without elevations at baseline) in
493 alkaline phosphatase and 27.5% (n=46) had postbaseline elevations in transaminases at

494 any time (not necessarily concurrent). The majority of these patients, 64.5% (n=20) and
495 71.7% (n=33), had liver metastases at baseline. In addition, 57.5% (n=96) and 35.3%
496 (n=59) of the 167 patients had elevations (grades 1 to 4) at both prebaseline and
497 postbaseline in alkaline phosphatase or transaminases, respectively. Only 7.8% (n=13)
498 and 3.0% (n=5) had grade 3 or 4 elevations in alkaline phosphatase or transaminases.

499 In the 596 patients treated with XELODA as first-line therapy for metastatic colorectal
500 cancer, the incidence of grade 3 or 4 hyperbilirubinemia was similar to the overall
501 clinical trial safety database of XELODA monotherapy. The median time to onset for
502 grade 3 or 4 hyperbilirubinemia in the colorectal cancer population was 64 days and
503 median total bilirubin increased from 8 µm/L at baseline to 13 µm/L during treatment
504 with XELODA. Of the 136 colorectal cancer patients with grade 3 or 4
505 hyperbilirubinemia, 49 patients had grade 3 or 4 hyperbilirubinemia as their last
506 measured value, of which 46 had liver metastases at baseline.

507 In 251 patients with metastatic breast cancer who received a combination of XELODA
508 and docetaxel, grade 3 (1.5 to 3 x ULN) hyperbilirubinemia occurred in 7% (n=17) and
509 grade 4 (>3 x ULN) hyperbilirubinemia occurred in 2% (n=5).

510 If drug-related grade 2 to 4 elevations in bilirubin occur, administration of XELODA
511 should be immediately interrupted until the hyperbilirubinemia resolves or decreases in
512 intensity to grade 1. NCIC grade 2 hyperbilirubinemia is defined as 1.5 x normal, grade 3
513 hyperbilirubinemia as 1.5 to 3 x normal and grade 4 hyperbilirubinemia as >3 x normal.
514 (See recommended dose modifications under **DOSAGE AND ADMINISTRATION**.)

515 Hematologic

516 In 875 patients with either metastatic breast or colorectal cancer who received a dose of
517 1250 mg/m² administered twice daily as monotherapy for 2 weeks followed by a 1-week
518 rest period, 3.2%, 1.7%, and 2.4% of patients had grade 3 or 4 neutropenia,
519 thrombocytopenia or decreases in hemoglobin, respectively. In 251 patients with
520 metastatic breast cancer who received a dose of XELODA in combination with
521 docetaxel, 68% had grade 3 or 4 neutropenia, 2.8% had grade 3 or 4 thrombocytopenia,
522 and 9.6% had grade 3 or 4 anemia.

523 Carcinogenesis, Mutagenesis and Impairment of Fertility

524 Adequate studies investigating the carcinogenic potential of XELODA have not been
525 conducted. Capecitabine was not mutagenic in vitro to bacteria (Ames test) or
526 mammalian cells (Chinese hamster V79/HPRT gene mutation assay). Capecitabine was
527 clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic in vivo to
528 mouse bone marrow (micronucleus test). Fluorouracil causes mutations in bacteria and
529 yeast. Fluorouracil also causes chromosomal abnormalities in the mouse micronucleus
530 test in vivo.

531 Impairment of Fertility

532 In studies of fertility and general reproductive performance in mice, oral capecitabine
533 doses of 760 mg/kg/day disturbed estrus and consequently caused a decrease in fertility.
534 In mice that became pregnant, no fetuses survived this dose. The disturbance in estrus

535 was reversible. In males, this dose caused degenerative changes in the testes, including
536 decreases in the number of spermatocytes and spermatids. In separate pharmacokinetic
537 studies, this dose in mice produced 5'-DFUR AUC values about 0.7 times the
538 corresponding values in patients administered the recommended daily dose.

539 **Information for Patients (see Patient Package Insert)**

540 Patients and patients' caregivers should be informed of the expected adverse effects of
541 XELODA, particularly nausea, vomiting, diarrhea, and hand-and-foot syndrome, and
542 should be made aware that patient-specific dose adaptations during therapy are expected
543 and necessary (see **DOSAGE AND ADMINISTRATION**). Patients should be
544 encouraged to recognize the common grade 2 toxicities associated with XELODA
545 treatment.

546 **Diarrhea**

547 Patients experiencing grade 2 diarrhea (an increase of 4 to 6 stools/day or nocturnal
548 stools) or greater should be instructed to stop taking XELODA immediately. Standard
549 antidiarrheal treatments (eg, loperamide) are recommended.

550 **Nausea**

551 Patients experiencing grade 2 nausea (food intake significantly decreased but able to eat
552 intermittently) or greater should be instructed to stop taking XELODA immediately.
553 Initiation of symptomatic treatment is recommended.

554 **Vomiting**

555 Patients experiencing grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater
556 should be instructed to stop taking XELODA immediately. Initiation of symptomatic
557 treatment is recommended.

558 **Hand-and-Foot Syndrome**

559 Patients experiencing grade 2 hand-and-foot syndrome (painful erythema and swelling of
560 the hands and/or feet and/or discomfort affecting the patients' activities of daily living) or
561 greater should be instructed to stop taking XELODA immediately.

562 **Stomatitis**

563 Patients experiencing grade 2 stomatitis (painful erythema, edema or ulcers of the mouth
564 or tongue, but able to eat) or greater should be instructed to stop taking XELODA
565 immediately. Initiation of symptomatic treatment is recommended (see **DOSAGE AND**
566 **ADMINISTRATION**).

567 **Fever and Neutropenia:**

568 Patients who develop a fever of 100.5°F or greater or other evidence of potential
569 infection should be instructed to call their physician.

570 **Drug-Food Interaction**

571 In all clinical trials, patients were instructed to administer XELODA within 30 minutes
572 after a meal. Since current safety and efficacy data are based upon administration with
573 food, it is recommended that XELODA be administered with food (see **DOSAGE AND**
574 **ADMINISTRATION**).

575 **Drug-Drug Interactions**

576 **Antacid**

577 The effect of an aluminum hydroxide- and magnesium hydroxide-containing antacid
578 (Maalox) on the pharmacokinetics of XELODA was investigated in 12 cancer patients.
579 There was a small increase in plasma concentrations of XELODA and one metabolite
580 (5'-DFCR); there was no effect on the 3 major metabolites (5'-DFUR, 5-FU and FBAL).

581 **Anticoagulants**

582 Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant
583 therapy should have their anticoagulant response (INR or prothrombin time) monitored
584 closely with great frequency and the anticoagulant dose should be adjusted accordingly
585 (see **Boxed WARNING** and **CLINICAL PHARMACOLOGY**). Altered coagulation
586 parameters and/or bleeding have been reported in patients taking XELODA
587 concomitantly with coumarin-derivative anticoagulants such as warfarin and
588 phenprocoumon. These events occurred within several days and up to several months
589 after initiating XELODA therapy and, in a few cases, within 1 month after stopping
590 XELODA. These events occurred in patients with and without liver metastases. In a drug
591 interaction study with single-dose warfarin administration, there was a significant
592 increase in the mean AUC of S-warfarin. The maximum observed INR value increased
593 by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by
594 capecitabine and/or its metabolites (see **CLINICAL PHARMACOLOGY**).

595 **CYP2C9 substrates**

596 Other than warfarin, no formal drug-drug interaction studies between XELODA and
597 other CYP2C9 substrates have been conducted. Care should be exercised when
598 XELODA is coadministered with CYP2C9 substrates.

599 **Phenytoin**

600 The level of phenytoin should be carefully monitored in patients taking XELODA and
601 phenytoin dose may need to be reduced (see **DOSAGE AND ADMINISTRATION:**
602 **Dose Management Guidelines**). Postmarketing reports indicate that some patients
603 receiving XELODA and phenytoin had toxicity associated with elevated phenytoin
604 levels. Formal drug-drug interaction studies with phenytoin have not been conducted, but
605 the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by
606 capecitabine and/or its metabolites (see **PRECAUTIONS: Drug-Drug Interactions:**
607 **Anticoagulants**).

608 Leucovorin
609 The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by
610 leucovorin. Deaths from severe enterocolitis, diarrhea, and dehydration have been
611 reported in elderly patients receiving weekly leucovorin and fluorouracil.

612 **Pregnancy**

613 **Teratogenic Effects**

614 Category D (see **WARNINGS**). Women of childbearing potential should be advised to
615 avoid becoming pregnant while receiving treatment with XELODA.

616 **Nursing Women**

617 Lactating mice given a single oral dose of capecitabine excreted significant amounts of
618 capecitabine metabolites into the milk. Because of the potential for serious adverse
619 reactions in nursing infants from capecitabine, it is recommended that nursing be
620 discontinued when receiving XELODA therapy.

621 **Pediatric Use**

622 The safety and effectiveness of XELODA in persons <18 years of age have not been
623 established.

624 **Geriatric Use**

625 Physicians should pay particular attention to monitoring the adverse effects of XELODA
626 in the elderly (see **WARNINGS: Geriatric Patients**).

627 **ADVERSE REACTIONS**

628 **Adjuvant Colon Cancer**

629 **Table 11** shows the adverse events occurring in $\geq 5\%$ of patients from one phase 3 trial in
630 patients with Dukes' C colon cancer who received at least one dose of study medication
631 and had at least one safety assessment. A total of 995 patients were treated with 1250
632 mg/m^2 twice a day of XELODA administered for 2 weeks followed by a 1-week rest
633 period, and 974 patients were administered 5-FU and leucovorin ($20 \text{ mg}/\text{m}^2$ leucovorin
634 IV followed by $425 \text{ mg}/\text{m}^2$ IV bolus 5-FU, on days 1-5, every 28 days). The median
635 duration of treatment was 164 days for capecitabine-treated patients and 145 days for 5-
636 FU/LV-treated patients. A total of 112 (11%) and 73 (7%) capecitabine and 5-FU/LV-
637 treated patients, respectively, discontinued treatment because of adverse events. A total of
638 18 deaths due to all causes occurred either on study or within 28 days of receiving study
639 drug: 8 (0.8%) patients randomized to XELODA and 10 (1.0%) randomized to 5-FU/LV.

640 **Table 12** shows grade 3/4 laboratory abnormalities occurring in $\geq 1\%$ of patients from
641 one phase 3 trial in patients with Dukes' C colon cancer who received at least one dose of
642 study medication and had at least one safety assessment.

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Table 11 Percent Incidence of Adverse Events Reported in $\geq 5\%$ of Patients Treated With XELODA or 5-FU/LV for Colon Cancer in the Adjuvant Setting (Safety Population)

Body System/ Adverse Event	Adjuvant Treatment for Colon Cancer (N=1969)			
	XELODA (N=995)		5-FU/LV (N=974)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
<i>Gastrointestinal Disorders</i>				
Diarrhea	47	12	65	14
Nausea	34	2	47	2
Stomatitis	22	2	60	14
Vomiting	15	2	21	2
Abdominal Pain	14	3	16	2
Constipation	9	-	11	<1
Upper Abdominal Pain	7	<1	7	<1
Dyspepsia	6	<1	5	-
<i>Skin and Subcutaneous Tissue Disorders</i>				
Hand-Foot Syndrome	60	17	9	<1
Alopecia	6	-	22	<1
Rash	7	-	8	-
Erythema	6	1	5	<1
<i>General Disorders and Administration Site Conditions</i>				
Fatigue	16	<1	16	1
Pyrexia	7	<1	9	<1
Asthenia	10	<1	10	1
Lethargy	10	<1	9	<1
<i>Nervous System Disorders</i>				
Dizziness	6	<1	6	-
Headache	5	<1	6	<1
Dysgeusia	6	-	9	-
<i>Metabolism and Nutrition Disorders</i>				
Anorexia	9	<1	11	<1
<i>Eye Disorders</i>				

Conjunctivitis	5	<1	6	<1
<i>Blood and Lymphatic System Disorders</i>				
Neutropenia	2	<1	8	5
<i>Respiratory Thoracic and Mediastinal Disorders</i>				
Epistaxis	2	-	5	-

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Table 12 Percent Incidence of Grade 3/4 Laboratory Abnormalities Reported in $\geq 1\%$ of Patients Receiving XELODA Monotherapy for Adjuvant Treatment of Colon Cancer (Safety Population)

Adverse Event	XELODA (n=995) Grade 3/4 %	IV 5-FU/LV (n= 974) Grade 3/4 %
Increased ALAT (SGPT)	1.6	0.6
Increased calcium	1.1	0.7
Decreased calcium	2.3	2.2
Decreased hemoglobin	1.0	1.2
Decreased lymphocytes	13.0	13.0
Decreased neutrophils*	2.2	26.2
Decreased neutrophils/granulocytes	2.4	26.4
Decreased platelets	1.0	0.7
Increased bilirubin**	20	6.3

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*The incidence of grade 3/4 white blood cell abnormalities was 1.3% in the XELODA arm and 4.9% in the IV 5-FU/LV arm.

**It should be noted that grading was according to NCIC CTC Version 1 (May, 1994). In the NCIC-CTC Version 1, hyperbilirubinemia grade 3 indicates a bilirubin value of 1.5 to 3.0 \times upper limit of normal (ULN) range, and grade 4 a value of $> 3.0 \times$ ULN. The NCI CTC Version 2 and above define a grade 3 bilirubin value of >3.0 to $10.0 \times$ ULN, and grade 4 values $>10.0 \times$ ULN.

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Metastatic Colorectal Cancer

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Table 13 shows the adverse events occurring in $\geq 5\%$ of patients from pooling the two phase 3 trials in first line metastatic colorectal cancer. A total of 596 patients with metastatic colorectal cancer were treated with 1250 mg/m² twice a day of XELODA administered for 2 weeks followed by a 1-week rest period, and 593 patients were administered 5-FU and leucovorin in the Mayo regimen (20 mg/m² leucovorin IV followed by 425 mg/m² IV bolus 5-FU, on days 1-5, every 28 days). In the pooled colorectal database the median duration of treatment was 139 days for capecitabine-treated patients and 140 days for 5-FU/LV-treated patients. A total of 78 (13%) and 63 (11%) capecitabine and 5-FU/LV-treated patients, respectively, discontinued treatment

669 because of adverse events/intercurrent illness. A total of 82 deaths due to all causes
 670 occurred either on study or within 28 days of receiving study drug: 50 (8.4%) patients
 671 randomized to XELODA and 32 (5.4%) randomized to 5-FU/LV.

672 **Table 13 Pooled Phase 3 Colorectal Trials:**
 673 **Percent Incidence of Adverse Events in ≥5% of Patients**

Adverse Event	XELODA (n=596)			5-FU/LV (n=593)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Number of Patients With > One Adverse Event	96	52	9	94	45	9
Body System/Adverse Event						
<i>GI</i>						
Diarrhea	55	13	2	61	10	2
Nausea	43	4	–	51	3	<1
Vomiting	27	4	<1	30	4	<1
Stomatitis	25	2	<1	62	14	1
Abdominal Pain	35	9	<1	31	5	–
Gastrointestinal Motility Disorder	10	<1	–	7	<1	–
Constipation	14	1	<1	17	1	–
Oral Discomfort	10	–	–	10	–	–
Upper GI Inflammatory Disorders	8	<1	–	10	1	–
Gastrointestinal Hemorrhage	6	1	<1	3	1	–
Ileus	6	4	1	5	2	1
<i>Skin and Subcutaneous</i>						
Hand-and-Foot Syndrome	54	17	NA	6	1	NA
Dermatitis	27	1	–	26	1	–
Skin Discoloration	7	<1	–	5	–	–
Alopecia	6	–	–	21	<1	–
<i>General</i>						
Fatigue/Weakness	42	4	–	46	4	–
Pyrexia	18	1	–	21	2	–
Edema	15	1	–	9	1	–
Pain	12	1	–	10	1	–
Chest Pain	6	1	–	6	1	<1
<i>Neurological</i>						
Peripheral Sensory Neuropathy	10	–	–	4	–	–
Headache	10	1	–	7	–	–
Dizziness*	8	<1	–	8	<1	–
Insomnia	7	–	–	7	–	–
Taste Disturbance	6	1	–	11	<1	1

Adverse Event	XELODA (n=596)			5-FU/LV (n=593)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Metabolism						
Appetite Decreased	26	3	<1	31	2	<1
Dehydration	7	2	<1	8	3	1
Eye						
Eye Irritation	13	–	–	10	<1	–
Vision Abnormal	5	–	–	2	–	–
Respiratory						
Dyspnea	14	1	–	10	<1	1
Cough	7	<1	1	8	–	–
Pharyngeal Disorder	5	–	–	5	–	–
Epistaxis	3	<1	–	6	–	–
Sore Throat	2	–	–	6	–	–
Musculoskeletal						
Back Pain	10	2	–	9	<1	–
Arthralgia	8	1	–	6	1	–
Vascular						
Venous Thrombosis	8	3	<1	6	2	–
Psychiatric						
Mood Alteration	5	–	–	6	<1	–
Depression	5	–	–	4	<1	–
Infections						
Viral	5	<1	–	5	<1	–
Blood and Lymphatic						
Anemia	80	2	<1	79	1	<1
Neutropenia	13	1	2	46	8	13
Hepatobiliary						
Hyperbilirubinemia	48	18	5	17	3	3

674
675
676
677

– Not observed
* Excluding vertigo
NA = Not Applicable

678 Breast Cancer Combination

679 The following data are shown for the combination study with XELODA and docetaxel in
680 patients with metastatic breast cancer in **Table 14** and **Table 15**. In the XELODA and
681 docetaxel combination arm the treatment was XELODA administered orally 1250 mg/m²
682 twice daily as intermittent therapy (2 weeks of treatment followed by 1 week without
683 treatment) for at least 6 weeks and docetaxel administered as a 1-hour intravenous
684 infusion at a dose of 75 mg/m² on the first day of each 3-week cycle for at least 6 weeks.

685 In the monotherapy arm docetaxel was administered as a 1-hour intravenous infusion at a
 686 dose of 100 mg/m² on the first day of each 3-week cycle for at least 6 weeks. The mean
 687 duration of treatment was 129 days in the combination arm and 98 days in the
 688 monotherapy arm. A total of 66 patients (26%) in the combination arm and 49 (19%) in
 689 the monotherapy arm withdrew from the study because of adverse events. The percentage
 690 of patients requiring dose reductions due to adverse events was 65% in the combination
 691 arm and 36% in the monotherapy arm. The percentage of patients requiring treatment
 692 interruptions due to adverse events in the combination arm was 79%. Treatment
 693 interruptions were part of the dose modification scheme for the combination therapy arm
 694 but not for the docetaxel monotherapy-treated patients.

695 **Table 14** **Percent Incidence of Adverse Events Considered Related or**
 696 **Unrelated to Treatment in ≥5% of Patients Participating in**
 697 **the XELODA and Docetaxel Combination vs Docetaxel**
 698 **Monotherapy Study**

Adverse Event	XELODA 1250 mg/m ² /bid With Docetaxel 75 mg/m ² /3 weeks (n=251)			Docetaxel 100 mg/m ² /3 weeks (n=255)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Number of Patients With at Least One Adverse Event	99	76.5	29.1	97	57.6	31.8
Body System/Adverse Event						
<i>GI</i>						
Diarrhea	67	14	<1	48	5	<1
Stomatitis	67	17	<1	43	5	–
Nausea	45	7	–	36	2	–
Vomiting	35	4	1	24	2	–
Constipation	20	2	–	18	–	–
Abdominal Pain	30	<3	<1	24	2	–
Dyspepsia	14	–	–	8	1	–
Dry Mouth	6	<1	–	5	–	–
<i>Skin and Subcutaneous</i>						
Hand-and-Foot Syndrome	63	24	NA	8	1	NA
Alopecia	41	6	–	42	7	–
Nail Disorder	14	2	–	15	–	–
Dermatitis	8	–	–	11	1	–
Rash Erythematous	9	<1	–	5	–	–
Nail Discoloration	6	–	–	4	<1	–
Onycholysis	5	1	–	5	1	–
Pruritus	4	–	–	5	–	–

Adverse Event	XELODA 1250 mg/m ² /bid With Docetaxel 75 mg/m ² /3 weeks (n=251)			Docetaxel 100 mg/m ² /3 weeks (n=255)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
General						
Pyrexia	28	2	–	34	2	–
Asthenia	26	4	<1	25	6	–
Fatigue	22	4	–	27	6	–
Weakness	16	2	–	11	2	–
Pain in Limb	13	<1	–	13	2	–
Lethargy	7	–	–	6	2	–
Pain	7	<1	–	5	1	–
Chest Pain (non-cardiac)	4	<1	–	6	2	–
Influenza-like Illness	5	–	–	5	–	–
Neurological						
Taste Disturbance	16	<1	–	14	<1	–
Headache	15	3	–	15	2	–
Paresthesia	12	<1	–	16	1	–
Dizziness	12	–	–	8	<1	–
Insomnia	8	–	–	10	<1	–
Peripheral Neuropathy	6	–	–	10	1	–
Hypoaesthesia	4	<1	–	8	<1	–
Metabolism						
Anorexia	13	1	–	11	<1	–
Appetite Decreased	10	–	–	5	–	–
Weight Decreased	7	–	–	5	–	–
Dehydration	10	2	–	7	<1	<1
Eye						
Lacrimation Increased	12	–	–	7	<1	–
Conjunctivitis	5	–	–	4	–	–
Eye Irritation	5	–	–	1	–	–
Musculoskeletal						
Arthralgia	15	2	–	24	3	–
Myalgia	15	2	–	25	2	–
Back Pain	12	<1	–	11	3	–
Bone Pain	8	<1	–	10	2	–
Cardiac						
Edema	33	<2	–	34	<3	1

Adverse Event	XELODA 1250 mg/m ² /bid With Docetaxel 75 mg/m ² /3 weeks (n=251)			Docetaxel 100 mg/m ² /3 weeks (n=255)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Blood						
Neutropenic Fever	16	3	13	21	5	16
Respiratory						
Dyspnea	14	2	<1	16	2	–
Cough	13	1	–	22	<1	–
Sore Throat	12	2	–	11	<1	–
Epistaxis	7	<1	–	6	–	–
Rhinorrhea	5	–	–	3	–	–
Pleural Effusion	2	1	–	7	4	–
Infection						
Oral Candidiasis	7	<1	–	8	<1	–
Urinary Tract Infection	6	<1	–	4	–	–
Upper Respiratory Tract	4	–	–	5	1	–
Vascular						
Flushing	5	–	–	5	–	–
Lymphoedema	3	<1	–	5	1	–
Psychiatric						
Depression	5	–	–	5	1	–

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701

– Not observed
NA = Not Applicable

702
703
704

Table 15 Percent of Patients With Laboratory Abnormalities Participating in the XELODA and Docetaxel Combination vs Docetaxel Monotherapy Study

Adverse Event	XELODA 1250 mg/m ² /bid With Docetaxel 75 mg/m ² / 3 weeks (n=251)			Docetaxel 100 mg/m ² / 3 weeks (n=255)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Hematologic						
Leukopenia	91	37	24	88	42	33
Neutropenia/Granulocytopenia	86	20	49	87	10	66
Thrombocytopenia	41	2	1	23	1	2
Anemia	80	7	3	83	5	<1
Lymphocytopenia	99	48	41	98	44	40
Hepatobiliary						
Hyperbilirubinemia	20	7	2	6	2	2

705

706 **Breast Cancer XELODA Monotherapy**

707 The following data are shown for the study in stage IV breast cancer patients who
 708 received a dose of 1250 mg/m² administered twice daily for 2 weeks followed by a
 709 1-week rest period. The mean duration of treatment was 114 days. A total of 13 out of
 710 162 patients (8%) discontinued treatment because of adverse events/intercurrent illness.

711 **Table 16 Percent Incidence of Adverse Events Considered Remotely,**
 712 **Possibly or Probably Related to Treatment in ≥5% of**
 713 **Patients Participating in the Single Arm Trial in Stage IV**
 714 **Breast Cancer**

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
	Body System/Adverse Event	Total %	Grade 3 %
<i>GI</i>			
Diarrhea	57	12	3
Nausea	53	4	–
Vomiting	37	4	–
Stomatitis	24	7	–
Abdominal Pain	20	4	–
Constipation	15	1	–
Dyspepsia	8	–	–
<i>Skin and Subcutaneous</i>			
Hand-and-Foot Syndrome	57	11	NA
Dermatitis	37	1	–
Nail Disorder	7	–	–
<i>General</i>			
Fatigue	41	8	–
Pyrexia	12	1	–
Pain in Limb	6	1	–
<i>Neurological</i>			
Paresthesia	21	1	–
Headache	9	1	–
Dizziness	8	–	–
Insomnia	8	–	–
<i>Metabolism</i>			
Anorexia	23	3	–
Dehydration	7	4	1
<i>Eye</i>			
Eye Irritation	15	–	–
<i>Musculoskeletal</i>			
Myalgia	9	–	–

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
Body System/Adverse Event	Total %	Grade 3 %	Grade 4 %
Cardiac Edema	9	1	–
Blood Neutropenia Thrombocytopenia Anemia Lymphopenia	26 24 72 94	2 3 3 44	2 1 1 15
Hepatobiliary Hyperbilirubinemia	22	9	2

715 – Not observed

716 NA = Not Applicable

717 **XELODA and Docetaxel in Combination**

718 Shown below by body system are the clinically relevant adverse events in <5% of
719 patients in the overall clinical trial safety database of 251 patients (Study Details)
720 reported as related to the administration of XELODA in combination with docetaxel and
721 that were clinically at least remotely relevant. In parentheses is the incidence of grade 3
722 and 4 occurrences of each adverse event.

723 It is anticipated that the same types of adverse events observed in the XELODA
724 monotherapy studies may be observed in patients treated with the combination of
725 XELODA plus docetaxel.

726 *Gastrointestinal:* ileus (0.39), necrotizing enterocolitis (0.39), esophageal ulcer (0.39),
727 hemorrhagic diarrhea (0.80)

728 *Neurological:* ataxia (0.39), syncope (1.20), taste loss (0.80), polyneuropathy (0.39),
729 migraine (0.39)

730 *Cardiac:* supraventricular tachycardia (0.39)

731 *Infection:* neutropenic sepsis (2.39), sepsis (0.39), bronchopneumonia (0.39)

732 *Blood and Lymphatic:* agranulocytosis (0.39), prothrombin decreased (0.39)

733 *Vascular:* hypotension (1.20), venous phlebitis and thrombophlebitis (0.39), postural
734 hypotension (0.80)

735 *Renal:* renal failure (0.39)

736 *Hepatobiliary:* jaundice (0.39), abnormal liver function tests (0.39), hepatic failure
737 (0.39), hepatic coma (0.39), hepatotoxicity (0.39)

738 *Immune System:* hypersensitivity (1.20)

739 **XELODA Monotherapy Metastatic Breast and Colorectal Cancer**

740 Shown below by body system are the clinically relevant adverse events in <5% of
741 patients in the overall clinical trial safety database of 875 patients (phase 3 colorectal
742 studies — 596 patients, phase 2 colorectal study — 34 patients, phase 2 breast cancer
743 studies — 245 patients) reported as related to the administration of XELODA and that
744 were clinically at least remotely relevant. In parentheses is the incidence of grade 3 or 4
745 occurrences of each adverse event.

746 *Gastrointestinal:* abdominal distension, dysphagia, proctalgia, ascites (0.1), gastric ulcer
747 (0.1), ileus (0.3), toxic dilation of intestine, gastroenteritis (0.1)

748 *Skin and Subcutaneous:* nail disorder (0.1), sweating increased (0.1), photosensitivity
749 reaction (0.1), skin ulceration, pruritus, radiation recall syndrome (0.2)

750 *General:* chest pain (0.2), influenza-like illness, hot flushes, pain (0.1), hoarseness,
751 irritability, difficulty in walking, thirst, chest mass, collapse, fibrosis (0.1), hemorrhage,
752 edema, sedation

753 *Neurological:* insomnia, ataxia (0.5), tremor, dysphasia, encephalopathy (0.1), abnormal
754 coordination, dysarthria, loss of consciousness (0.2), impaired balance

755 *Metabolism:* increased weight, cachexia (0.4), hypertriglyceridemia (0.1), hypokalemia,
756 hypomagnesemia

757 *Eye:* conjunctivitis

758 *Respiratory:* cough (0.1), epistaxis (0.1), asthma (0.2), hemoptysis, respiratory distress
759 (0.1), dyspnea

760 *Cardiac:* tachycardia (0.1), bradycardia, atrial fibrillation, ventricular extrasystoles,
761 extrasystoles, myocarditis (0.1), pericardial effusion

762 *Infections:* laryngitis (1.0), bronchitis (0.2), pneumonia (0.2), bronchopneumonia (0.2),
763 keratoconjunctivitis, sepsis (0.3), fungal infections (including candidiasis) (0.2)

764 *Musculoskeletal:* myalgia, bone pain (0.1), arthritis (0.1), muscle weakness

765 *Blood and Lymphatic:* leukopenia (0.2), coagulation disorder (0.1), bone marrow
766 depression (0.1), idiopathic thrombocytopenia purpura (1.0), pancytopenia (0.1)

767 *Vascular:* hypotension (0.2), hypertension (0.1), lymphoedema (0.1), pulmonary
768 embolism (0.2), cerebrovascular accident (0.1)

769 *Psychiatric:* depression, confusion (0.1)

770 *Renal:* renal impairment (0.6)

771 *Ear:* vertigo

772 *Hepatobiliary:* hepatic fibrosis (0.1), hepatitis (0.1), cholestatic hepatitis (0.1), abnormal
773 liver function tests

774 *Immune System:* drug hypersensitivity (0.1)

775 **Postmarketing:** hepatic failure, lacrimal duct stenosis

776 **OVERDOSAGE**

777 The manifestations of acute overdose would include nausea, vomiting, diarrhea,
778 gastrointestinal irritation and bleeding, and bone marrow depression. Medical
779 management of overdose should include customary supportive medical interventions
780 aimed at correcting the presenting clinical manifestations. Although no clinical
781 experience using dialysis as a treatment for XELODA overdose has been reported,
782 dialysis may be of benefit in reducing circulating concentrations of 5'-DFUR, a low-
783 molecular-weight metabolite of the parent compound.

784 Single doses of XELODA were not lethal to mice, rats, and monkeys at doses up to
785 2000 mg/kg (2.4, 4.8, and 9.6 times the recommended human daily dose on a mg/m²
786 basis).

787 **DOSAGE AND ADMINISTRATION**

788 The recommended dose of XELODA is 1250 mg/m² administered orally twice daily
789 (morning and evening; equivalent to 2500 mg/m² total daily dose) for 2 weeks followed
790 by a 1-week rest period given as 3-week cycles. XELODA tablets should be swallowed
791 with water within 30 minutes after a meal. In combination with docetaxel, the
792 recommended dose of XELODA is 1250 mg/m² twice daily for 2 weeks followed by a
793 1-week rest period, combined with docetaxel at 75 mg/m² as a 1-hour intravenous
794 infusion every 3 weeks. Pre-medication, according to the docetaxel labeling, should be
795 started prior to docetaxel administration for patients receiving the XELODA plus
796 docetaxel combination. **Table 17** displays the total daily dose by body surface area and
797 the number of tablets to be taken at each dose.

798 Adjuvant treatment in patients with Dukes' C colon cancer is recommended for a total of
799 6 months, ie, XELODA 1250 mg/m² orally twice daily for 2 weeks followed by a 1-week
800 rest period, given as 3-week cycles for a total of 8 cycles (24 weeks).

801 **Table 17 XELODA Dose Calculation According to Body Surface Area**

Dose Level 1250 mg/m ² Twice a Day		Number of Tablets to be Taken at Each Dose (Morning and Evening)	
Surface Area (m ²)	Total Daily* Dose (mg)	150 mg	500 mg
≤ 1.25	3000	0	3
1.26 - 1.37	3300	1	3
1.38 - 1.51	3600	2	3
1.52 - 1.65	4000	0	4
1.66 - 1.77	4300	1	4
1.78 - 1.91	4600	2	4
1.92 - 2.05	5000	0	5
2.06 - 2.17	5300	1	5
≥ 2.18	5600	2	5

802 *Total Daily Dose divided by 2 to allow equal morning and evening doses

803

804 **Dose Management Guidelines**

805 XELODA dosage may need to be individualized to optimize patient management.
806 Patients should be carefully monitored for toxicity and doses of XELODA should be
807 modified as necessary to accommodate individual patient tolerance to treatment (see
808 **CLINICAL STUDIES**). Toxicity due to XELODA administration may be managed by
809 symptomatic treatment, dose interruptions and adjustment of XELODA dose. Once the
810 dose has been reduced it should not be increased at a later time.

811 The dose of phenytoin and the dose of coumarin-derivative anticoagulants may need to
812 be reduced when either drug is administered concomitantly with XELODA (see
813 **PRECAUTIONS: Drug-Drug Interactions**).

814 XELODA dose modification scheme as described below (see **Table 18** and **Table 19**) is
815 recommended for the management of adverse events.

816 **Table 18 XELODA in Combination With Docetaxel Dose Reduction**
817 **Schedule**

Toxicity NCIC Grades*	Grade 2	Grade 3	Grade 4
1st appearance	Grade 2 occurring during the 14 days of XELODA treatment: interrupt XELODA treatment until resolved to grade 0-1. Treatment may be resumed during the cycle at the same dose of XELODA. Doses of XELODA missed during a treatment cycle are not to be replaced. Prophylaxis for toxicities should be implemented where possible. Grade 2 persisting at the time the next XELODA/docetaxel treatment is due: delay treatment until resolved to grade 0-1, then continue at 100% of the original XELODA and docetaxel dose. Prophylaxis for toxicities should be implemented where possible.	Grade 3 occurring during the 14 days of XELODA treatment: interrupt the XELODA treatment until resolved to grade 0-1. Treatment may be resumed during the cycle at 75% of the XELODA dose. Doses of XELODA missed during a treatment cycle are not to be replaced. Prophylaxis for toxicities should be implemented where possible. Grade 3 persisting at the time the next XELODA/docetaxel treatment is due: delay treatment until resolved to grade 0-1. For patients developing grade 3 toxicity at any time during the treatment cycle, upon resolution to grade 0-1, subsequent treatment cycles should be continued at 75% of the original XELODA dose and at 55	Discontinue treatment unless treating physician considers it to be in the best interest of the patient to continue with XELODA at 50% of original dose.

Toxicity NCIC Grades*	Grade 2	Grade 3	Grade 4
		mg/m ² of docetaxel. Prophylaxis for toxicities should be implemented where possible.	
2nd appearance of same toxicity	<p>Grade 2 occurring during the 14 days of XELODA treatment: interrupt XELODA treatment until resolved to grade 0-1. Treatment may be resumed during the cycle at 75% of original XELODA dose. Doses of XELODA missed during a treatment cycle are not to be replaced. Prophylaxis for toxicities should be implemented where possible.</p> <p>Grade 2 persisting at the time the next XELODA/docetaxel treatment is due: delay treatment until resolved to grade 0-1.</p> <p>For patients developing 2nd occurrence of grade 2 toxicity at any time during the treatment cycle, upon resolution to grade 0-1, subsequent treatment cycles should be continued at 75% of the original XELODA dose and at 55 mg/m² of docetaxel. Prophylaxis for toxicities should be implemented where possible.</p>	<p>Grade 3 occurring during the 14 days of XELODA treatment: interrupt the XELODA treatment until resolved to grade 0-1. Treatment may be resumed during the cycle at 50% of the XELODA dose. Doses of XELODA missed during a treatment cycle are not to be replaced. Prophylaxis for toxicities should be implemented where possible.</p> <p>Grade 3 persisting at the time the next XELODA/docetaxel treatment is due: delay treatment until resolved to grade 0-1.</p> <p>For patients developing grade 3 toxicity at any time during the treatment cycle, upon resolution to grade 0-1, subsequent treatment cycles should be continued at 50% of the original XELODA dose and the docetaxel discontinued. Prophylaxis for toxicities should be implemented where possible.</p>	Discontinue treatment.
3rd appearance of same toxicity	<p>Grade 2 occurring during the 14 days of XELODA treatment: interrupt XELODA treatment until resolved to grade 0-1. Treatment may be resumed during the cycle at 50% of the original XELODA dose. Doses of XELODA missed during a treatment cycle are not to be replaced.</p>	Discontinue treatment.	

Toxicity NCIC Grades*	Grade 2	Grade 3	Grade 4
	<p>Prophylaxis for toxicities should be implemented where possible.</p> <p>Grade 2 persisting at the time the next XELODA/docetaxel treatment is due: delay treatment until resolved to grade 0-1.</p> <p>For patients developing 3rd occurrence of grade 2 toxicity at any time during the treatment cycle, upon resolution to grade 0-1, subsequent treatment cycles should be continued at 50% of the original XELODA dose and the docetaxel discontinued. Prophylaxis for toxicities should be implemented where possible.</p>		
4th appearance of same toxicity	Discontinue treatment.		

818 *National Cancer Institute of Canada Common Toxicity Criteria were used except for hand-and-foot
819 syndrome (see **PRECAUTIONS**).
820

821 Dose modification for the use of XELODA as monotherapy is shown in **Table 19**.

822
823

Table 19 Recommended Dose Modifications with XELODA Monotherapy

Toxicity NCIC Grades*	During a Course of Therapy	Dose Adjustment for Next Treatment (% of starting dose)
• <i>Grade 1</i>	Maintain dose level	Maintain dose level
• <i>Grade 2</i>		
-1 st appearance	Interrupt until resolved to grade 0-1	100%
-2 nd appearance	Interrupt until resolved to grade 0-1	75%
-3 rd appearance	Interrupt until resolved to grade 0-1	50%
-4 th appearance	Discontinue treatment permanently	
• <i>Grade 3</i>		
-1 st appearance	Interrupt until resolved to grade 0-1	75%
-2 nd appearance	Interrupt until resolved to grade 0-1	50%
-3 rd appearance	Discontinue treatment permanently	
• <i>Grade 4</i>		
-1 st appearance	Discontinue permanently <i>OR</i> If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

824 *National Cancer Institute of Canada Common Toxicity Criteria were used except for the hand-and-foot
825 syndrome (see **PRECAUTIONS**).
826

827 Dosage modifications are not recommended for grade 1 events. Therapy with XELODA
828 should be interrupted upon the occurrence of a grade 2 or 3 adverse experience. Once the
829 adverse event has resolved or decreased in intensity to grade 1, then XELODA therapy
830 may be restarted at full dose or as adjusted according to **Table 18** and **Table 19**. If a
831 grade 4 experience occurs, therapy should be discontinued or interrupted until resolved or
832 decreased to grade 1, and therapy should be restarted at 50% of the original dose. Doses
833 of XELODA omitted for toxicity are not replaced or restored; instead the patient should
834 resume the planned treatment cycles.

835 **Adjustment of Starting Dose in Special Populations**

836 **Hepatic Impairment**

837 In patients with mild to moderate hepatic dysfunction due to liver metastases, no starting
838 dose adjustment is necessary; however, patients should be carefully monitored. Patients
839 with severe hepatic dysfunction have not been studied.

840 **Renal Impairment**

841 No adjustment to the starting dose of XELODA is recommended in patients with mild
842 renal impairment (creatinine clearance = 51 to 80 mL/min [Cockcroft and Gault, as shown
843 below]). In patients with moderate renal impairment (baseline creatinine clearance = 30

844 to 50 mL/min), a dose reduction to 75% of the XELODA starting dose when used as
845 monotherapy or in combination with docetaxel (from 1250 mg/m² to 950 mg/m² twice
846 daily) is recommended (see **CLINICAL PHARMACOLOGY: Special Populations**).
847 Subsequent dose adjustment is recommended as outlined in **Table 18** and **Table 19** if a
848 patient develops a grade 2 to 4 adverse event (see **WARNINGS**). The starting dose
849 adjustment recommendations for patients with moderate renal impairment apply both to
850 XELODA monotherapy and XELODA in combination use with docetaxel.

851 Cockcroft and Gault Equation:

$$852 \qquad \qquad \qquad (140 - \text{age [yrs]}) (\text{body wt [kg]})$$
$$853 \quad \text{Creatinine clearance for males} = \frac{\qquad \qquad \qquad}{\qquad \qquad \qquad}$$
$$854 \qquad \qquad \qquad (72) (\text{serum creatinine [mg/dL]})$$

855 Creatinine clearance for females = 0.85 x male value

856 Geriatrics

857 Physicians should exercise caution in monitoring the effects of XELODA in the elderly.
858 Insufficient data are available to provide a dosage recommendation.

859 HOW SUPPLIED

860 XELODA is supplied as biconvex, oblong film-coated tablets, available in bottles as
861 follows:

862 **150 mg**

863 color: light peach

864 engraving: XELODA on one side, 150 on the other

865 150 mg tablets are packaged in bottles of 60 (NDC 0004-1100-20).

866 **500 mg**

867 color: peach

868 engraving: XELODA on one side, 500 on the other

869 500 mg tablets are packaged in bottles of 120 (NDC 0004-1101-50).

870 Storage Conditions

871 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP
872 Controlled Room Temperature]. KEEP TIGHTLY CLOSED.

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874 Taxotere is a registered trademark of Aventis Pharmaceuticals Inc.

875 For full Taxotere prescribing information, please refer to Taxotere Package Insert.

876

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Patient Information
XELODA® (capecitabine) TABLETS

RX ONLY

Read this leaflet before you start taking XELODA® [zeh-LOE-duh] and each time you refill your prescription in case the information has changed. This leaflet contains important information about XELODA. However, this information does not take the place of talking with your doctor. This information cannot cover all possible risks and benefits of XELODA. Your doctor should always be your first choice for discussing your medical condition and this medicine.

What is XELODA?

XELODA is a medicine you take by mouth (orally). XELODA is changed in the body to 5-fluorouracil (5-FU). In some patients with colon, rectum or breast cancer, 5-FU stops cancer cells from growing and decreases the size of the tumor.

XELODA is used to treat:

- cancer of the colon after surgery
- cancer of the colon or rectum (colorectal cancer) that has spread to other parts of the body (metastatic colorectal cancer). You should know that in studies, other medicines showed improved survival when they were taken together with 5-FU and leucovorin. In studies, XELODA was no worse than 5-FU and leucovorin taken together but did not improve survival compared to these two medicines.
- breast cancer that has spread to other parts of the body (metastatic breast cancer) together with another medicine called docetaxel (Taxotere®)
- breast cancer that has spread to other parts of the body and has not improved after treatment with other medicines such as paclitaxel (Taxol®) and anthracycline-containing medicine such as Adriamycin® and doxorubicin

What is the most important information about XELODA?

XELODA may increase the effect of other medicines used to thin your blood such as warfarin (Coumadin®). It is very important that your doctor knows if you are taking a blood thinner such as warfarin because XELODA may increase the effect of this medicine and could lead to serious side effects. If you are taking blood thinners and XELODA, your doctor needs to check more often how fast your blood clots and change the dose of the blood thinner, if needed.

36 **Who should not take XELODA?**

37 **1. DO NOT TAKE XELODA IF YOU**

- 38 – are nursing a baby. Tell your doctor if you are nursing. XELODA may pass to the
- 39 baby in your milk and harm the baby.
- 40 – are allergic to 5-fluorouracil
- 41 – are allergic to capecitabine or to any of the ingredients in XELODA
- 42 – have been told that you lack the enzyme DPD (dihydropyrimidine dehydrogenase)

43 **2. TELL YOUR DOCTOR IF YOU**

- 44 – take a blood thinner such as warfarin (Coumadin). This is very important because
- 45 XELODA may increase the effect of the blood thinner. If you are taking blood
- 46 thinners and XELODA, your doctor needs to check more often how fast your blood
- 47 clots and change the dose of the blood thinner, if needed.
- 48 – take phenytoin (Dilantin[®]). Your doctor needs to test the levels of phenytoin in your
- 49 blood more often or change your dose of phenytoin.
- 50 – are pregnant or think you may be pregnant. XELODA may harm your unborn child.
- 51 – have kidney problems. Your doctor may prescribe a different medicine or lower the
- 52 XELODA dose.
- 53 – have liver problems. You may need to be checked for liver problems while you take
- 54 XELODA.
- 55 – have heart problems because you could have more side effects related to your heart.
- 56 – take the vitamin folic acid. It may affect how XELODA works.

57 **How should I take XELODA?**

58 Take XELODA exactly as your doctor tells you to. Your doctor will prescribe a dose and
59 treatment plan that is right for *you*. Your doctor may want you to take both 150 mg and
60 500 mg tablets together for each dose. If so, you must be able to identify the tablets.
61 Taking the wrong tablets could cause an overdose (too much medicine) or underdose (too
62 little medicine). The 150 mg tablets are light peach in color with 150 on one side. The
63 500 mg tablets are peach in color with 500 on one side. Your doctor may change the
64 amount of medicine you take during your treatment. Your doctor may prescribe
65 XELODA Tablets with Taxotere or docetaxel injection.

- 66 – XELODA is taken in 2 daily doses, a morning dose and an evening dose
- 67 – Take XELODA tablets **within 30 minutes after the end of a meal** (breakfast and
- 68 dinner)
- 69 – **Swallow XELODA tablets with water**
- 70 – If you miss a dose of XELODA, do not take the missed dose at all and do not double
- 71 the next dose. Instead, continue your regular dosing schedule and check with your
- 72 doctor.
- 73 – XELODA is usually taken for 14 days followed by a 7-day rest period (no drug), for
- 74 a 21-day cycle. Your doctor will tell you how many cycles of treatment you will
- 75 need.
- 76 – If you take too much XELODA, contact your doctor or local poison control center or
- 77 emergency room **right away**.

78 **What should I avoid while taking XELODA?**

- 79 – Women should not become pregnant while taking XELODA. XELODA may harm
80 your unborn child. Use effective birth control while taking XELODA. Tell your
81 doctor if you become pregnant.
82 – Do not breast-feed. XELODA may pass through your milk and harm your baby
83 – Men should use birth control while taking XELODA

84 **What are the most common side effects of XELODA?**

85 The most common side effects of XELODA are:

- 86 – diarrhea, nausea, vomiting, sores in the mouth and throat (stomatitis), stomach area
87 pain (abdominal pain), upset stomach, constipation, loss of appetite, and too much
88 water loss from the body (dehydration). These side effects are more common in
89 patients age 80 and older.
90 – hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become
91 numb, painful, swollen or red), rash, dry, itchy or discolored skin, nail problems, and
92 hair loss
93 – tiredness, weakness, dizziness, headache, fever, pain (including chest, back, joint, and
94 muscle pain), trouble sleeping, and taste problems
95

96 These side effects may differ when taking XELODA with Taxotere. Please consult your
97 doctor for possible side effects that may be caused by taking XELODA with Taxotere.

98 If you are concerned about these or any other side effects while taking XELODA, talk to
99 your doctor.

100 **Stop taking XELODA immediately and contact your doctor right away** if you have
101 the side effects listed below, or other side effects that concern you. Your doctor can then
102 adjust XELODA to a dose that is right for you or stop your XELODA treatment for a
103 while. This should help to reduce the side effects and stop them from getting worse.

- 104 – **Diarrhea:** if you have an additional 4 bowel movements each day beyond what is
105 normal or any diarrhea at night
106 – **Vomiting:** if you vomit more than once in a 24-hour time period
107 – **Nausea:** if you lose your appetite, and the amount of food you eat each day is much
108 less than usual
109 – **Stomatitis:** if you have pain, redness, swelling or sores in your mouth
110 – **Hand-and-Foot Syndrome:** if you have pain, swelling or redness of your hands or
111 feet that prevents normal activity
112 – **Fever or Infection:** if you have a temperature of 100.5°F or greater, or other signs of
113 infection

114 Your doctor may tell you to lower the dose or to stop XELODA treatment for a while. If
115 caught early, most of these side effects usually improve after you stop taking XELODA.
116 If they do not improve within 2 to 3 days, call your doctor again. After your side effects
117 have improved, your doctor will tell you whether to start taking XELODA again and
118 what dose to take. Adjusting the dose of XELODA to be right for each patient is an
119 important part of treatment.

120 **How should I store and use XELODA?**

- 121 – Never share XELODA with anyone
- 122 – Store XELODA at normal room temperature (about 65° to 85°F)
- 123 – Keep XELODA and all other medicines out of the reach of children
- 124 – If you take too much XELODA by mistake, contact your doctor or local poison
125 control center or emergency room **right away**

126 **General advice about prescription medicines:**

127 Medicines are sometimes prescribed for conditions that are not mentioned in patient
128 information leaflets. Do not use XELODA for a condition for which it was not
129 prescribed. Do not give XELODA to other people, even if they have the same symptoms
130 you have. It may harm them.

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

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136 Adriamycin is a registered trademark of Bristol-Myers Squibb Company.

137 Coumadin is a registered trademark of Bristol-Myers Squibb Company.

138 Dilantin is a registered trademark of Parke-Davis.

139 Taxol is a registered trademark of Bristol-Myers Squibb Company.

140 Taxotere is a registered trademark of Aventis Pharmaceuticals Inc.

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Important Side Effect Information
XELODA[®]
(capecitabine) Tablets

STOP taking XELODA immediately and contact your doctor if any of these symptoms occur.



Moderate diarrhea.
(increase of 4-6 stools a day)



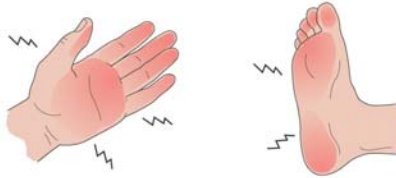
Diarrhea at night.



Moderate pain and redness of the mouth, swelling of the mouth or mouth sores.



Nausea and vomiting.



Moderate pain, swelling and redness of hands and/or feet.

If you have a temperature of 100.5°F or greater, or other signs of infection.

- If caught early, most of these side effects usually improve after you stop taking XELODA.
- If they do not improve within 2 to 3 days, call your doctor again.
- After side effects have improved, your doctor will tell you whether to start taking XELODA again or what dose to use.

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