



XELODA[®]
(capecitabine)
TABLETS

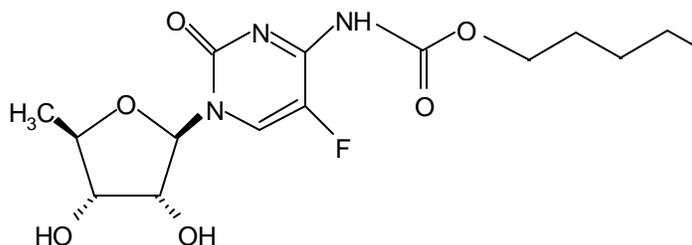
WARNING

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. Post-marketing 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 one 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 tablet contains 500 mg

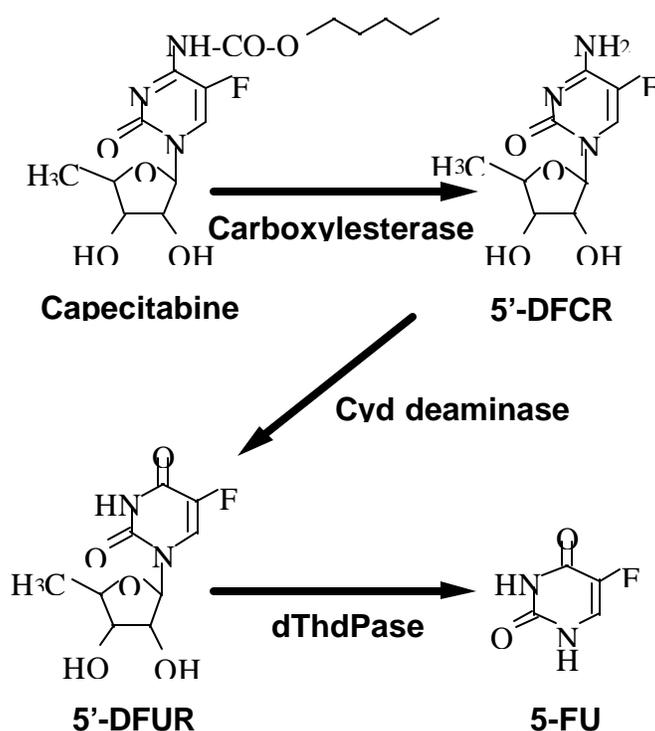
XELODA® (capecitabine)

16 capecitabine. The inactive ingredients in XELODA include: anhydrous lactose, croscarmellose sodium,
 17 hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The
 18 peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, and
 19 synthetic yellow and red iron oxides.

CLINICAL PHARMACOLOGY

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

23 **Bioactivation:** Capecitabine is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa
 24 carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine
 25 deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-
 26 deoxy-5-fluorouridine (5'-DFUR). The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes
 27 5'-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase.
 28 Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.

Metabolic Pathway of capecitabine to 5-FU

30

31 **Mechanism of Action:** Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine
 32 monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell
 33 injury by two different mechanisms. First, FdUMP and the folate cofactor, N^5 -¹⁰-
 34 methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary

XELODA[®] (capecitabine)

35 complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate. Thymidylate is the
36 necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a
37 deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can
38 mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This
39 metabolic error can interfere with RNA processing and protein synthesis.

40 **Pharmacokinetics in Colorectal Tumors and Adjacent Healthy Tissue:** Following oral
41 administration of XELODA 7 days before surgery in patients with colorectal cancer, the median ratio of
42 5-FU concentration in colorectal tumors to adjacent tissues was 2.9 (range from 0.9 to 8.0). These
43 ratios have not been evaluated in breast cancer patients or compared to 5-FU infusion.

44 **Human Pharmacokinetics:** The pharmacokinetics of XELODA and its metabolites have been
45 evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m²/day. Over this
46 range, the pharmacokinetics of XELODA and its metabolite, 5'-DFCR were dose proportional and did
47 not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than
48 proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1.
49 The elimination half-life of both parent capecitabine and 5-FU was about 3/4 of an hour. The inter-patient
50 variability in the C_{max} and AUC of 5-FU was greater than 85%.

51 **Absorption, Distribution, Metabolism and Excretion:** Capecitabine reached peak blood levels in
52 about 1.5 hours (T_{max}) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the
53 rate and extent of absorption of capecitabine with mean C_{max} and AUC_{0-∞} decreased by 60% and 35%,
54 respectively. The C_{max} and AUC_{0-∞} of 5-FU were also reduced by food by 43% and 21%, respectively.
55 Food delayed T_{max} of both parent and 5-FU by 1.5 hours (see PRECAUTIONS and DOSAGE AND
56 ADMINISTRATION).

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

59 Capecitabine is extensively metabolized enzymatically to 5-FU. The enzyme dihydropyrimidine
60 dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism, to the much less toxic 5-
61 fluoro-5, 6-dihydro-fluorouracil (FUH₂). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-
62 fluoro-ureido-propionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-
63 alanine (FBAL) which is cleared in the urine.

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

68 A clinical phase I study evaluating the effect of XELODA on the pharmacokinetics of docetaxel
69 (Taxotere[®]) and the effect of docetaxel on the pharmacokinetics of XELODA was conducted in 26
70 patients with solid tumors. XELODA was found to have no effect on the pharmacokinetics of docetaxel

XELODA[®] (capecitabine)

71 (C_{\max} and AUC) and docetaxel has no effect on the pharmacokinetics of capecitabine and the 5-FU
72 precursor 5'-DFUR.

73 *Special Populations:*

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

81 *Hepatic Insufficiency:* XELODA has been evaluated in 13 patients with mild to moderate hepatic
82 dysfunction due to liver metastases defined by a composite score including bilirubin, AST/ALT and
83 alkaline phosphatase following a single 1255 mg/m² dose of XELODA. Both AUC_{0-∞} and C_{max} of
84 capecitabine increased by 60% in patients with hepatic dysfunction compared to patients with normal
85 hepatic function (n=14). The AUC_{0-∞} and C_{max} of 5-FU was not affected. In patients with mild to
86 moderate hepatic dysfunction due to liver metastases, caution should be exercised when XELODA is
87 administered. The effect of severe hepatic dysfunction on XELODA is not known (see
88 PRECAUTIONS and DOSAGE AND ADMINISTRATION).

89 *Renal Insufficiency:* Following oral administration of 1250 mg/m² capecitabine twice a day to
90 cancer patients with varying degrees of renal impairment, patients with moderate (creatinine
91 clearance = 30-50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment
92 showed 85% and 258% higher systemic exposure to FBAL on day 1 compared to normal renal
93 function patients (creatinine clearance >80 mL/min). Systemic exposure to 5'-DFUR was 42%
94 and 71% greater in moderately and severely renal impaired patients, respectively, than in normal
95 patients. Systemic exposure to capecitabine was about 25% greater in both moderately and
96 severely renal impaired patients (see CONTRAINDICATIONS, WARNINGS, and DOSAGE
97 AND ADMINISTRATION).

98 *Drug-Drug Interactions:*

99 *Anticoagulants:* In four patients with cancer, chronic administration of capecitabine (1250 mg/ m² bid)
100 with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and decreased its
101 clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8 fold, and the
102 maximum observed mean INR value was increased by 91% (see Box WARNINGS and
103 PRECAUTIONS: *Drug-Drug Interactions*).

XELODA[®] (capecitabine)

104 *Drugs Metabolized by Cytochrome P450 Enzymes:* In vitro enzymatic studies with human liver
105 microsomes indicated that capecitabine and its metabolites (5'-DFUR, 5'-DFCR, 5-FU, and FBAL)
106 had no inhibitory effects on substrates of cytochrome P450 for the major isoenzymes such as 1A2,
107 2A6, 3A4, 2C9, 2C19, 2D6, and 2E1.

108 *Antacid:* When Maalox[®] (20 mL), an aluminum hydroxide- and magnesium hydroxide- containing
109 antacid, was administered immediately after XELODA (1250 mg/m², n=12 cancer patients), AUC and
110 C_{max} increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for
111 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of
112 XELODA.

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

114 CLINICAL STUDIES

115 *Colorectal Carcinoma:* The recommended dose of XELODA was determined in a open-label,
116 randomized clinical study, exploring the efficacy and safety of continuous therapy with
117 capecitabine (1331 mg/m²/day in two divided doses, n=39), intermittent therapy with
118 capecitabine (2510 mg/m²/day in two divided doses, n=34), and intermittent therapy with
119 capecitabine in combination with oral leucovorin (LV) (capecitabine 1657 mg/m²/day in two
120 divided doses, n=35; leucovorin 60 mg/day) in patients with advanced and/or metastatic
121 colorectal carcinoma in the first-line metastatic setting. There was no apparent advantage in
122 response rate to adding leucovorin to XELODA; however, toxicity was increased. XELODA,
123 1250 mg/m² twice daily for 14 days followed by a 1-week rest, was selected for further clinical
124 development based on the overall safety and efficacy profile of the three schedules studied.

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

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

139 The baseline demographics for XELODA and 5-FU/LV patients are shown in Table 1.

XELODA[®] (capecitabine)

140

Table 1. 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)

XELODA[®] (capecitabine)

141 The efficacy endpoints for the two phase 3 trials are shown in Tables 2 and 3.

142

Table 2. Efficacy of XELODA vs. 5-FU/LV in Colorectal Cancer

143

(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)	380 (321-434)	407 (366-446)
Hazard Ratio (XELODA/5-FU/LV) 95% C.I. for Hazard Ratio	1.00 0.84-1.18	

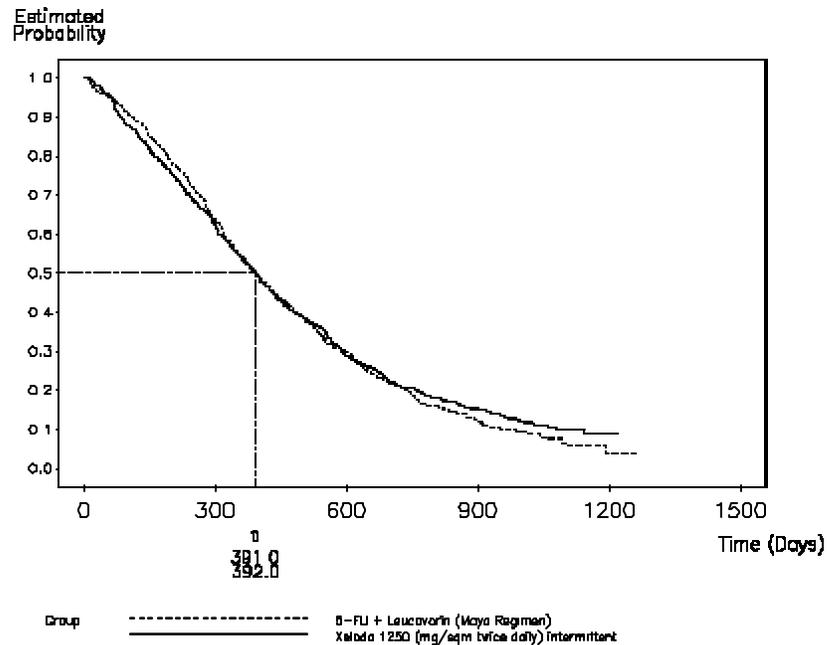
144

Table 3. Efficacy of XELODA vs. 5-FU/LV in Colorectal Cancer

145

(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) 95% C.I. for Hazard Ratio	0.97 0.82-1.14	
Survival (Median, days, 95% C.I.)	404 (367-452)	369 (338-430)
Hazard Ratio (XELODA/5-FU/LV) 95% C.I. for Hazard Ratio	0.92 0.78-1.09	

XELODA[®] (capecitabine)146 **Figure 1. Kaplan-Meier Curve for Overall Survival of Pooled Data (Studies 1 and 2)**

147

148 XELODA was superior to 5-FU/LV for objective response rate in Study 1 and Study 2. The similarity
 149 of XELODA and 5-FU/LV in these studies was assessed by examining the potential difference between
 150 the two treatments. In order to assure that XELODA has a clinically meaningful survival effect, statistical
 151 analyses were performed to determine the percent of the survival effect of 5-FU/LV that was retained
 152 by XELODA. The estimate of the survival effect of 5-FU/LV was derived from a meta-analysis of ten
 153 randomized studies from the published literature comparing 5-FU to regimens of 5-FU/LV that were
 154 similar to the control arms used in these Studies 1 and 2. The method for comparing the treatments was
 155 to examine the worst case (95% confidence upper bound) for the difference between 5-FU/LV and
 156 XELODA, and to show that loss of more than 50% of the 5-FU/LV survival effect was ruled out. It
 157 was demonstrated that the percent of the survival effect of 5-FU/LV maintained was at least 61% for
 158 Study 2 and 10% for Study 1. The pooled result is consistent with a retention of at least 50% of the
 159 effect of 5-FU/LV. It should be noted that these values for preserved effect are based on the upper
 160 bound of the 5-FU/LV vs. XELODA difference. These results do not exclude the possibility of true
 161 equivalence of XELODA to 5-FU/LV (see Tables 2 and 3 and Kaplan-Meier Figure 1).

162 **Breast Carcinoma:** XELODA has been evaluated in clinical trials in combination with docetaxel
 163 (Taxotere[®]) and as monotherapy.

164 **Breast Cancer Combination Therapy:** The dose of XELODA used in phase 3 clinical trial in
 165 combination with docetaxel was based on the results of a phase I study, where a range of doses of
 166 docetaxel administered in 3 week cycles in combination with an intermittent regimen of XELODA (14

XELODA[®] (capecitabine)

167 days of treatment, followed by a 7 day rest period) were evaluated. The combination dose regimen was
168 selected based on the tolerability profile of the 75 mg/m² administered in 3 week cycles of docetaxel in
169 combination with 1250 mg/m² twice daily for 14 days of XELODA administered in 3 week cycles. The
170 approved dose of 100 mg/m² of docetaxel administered in 3 week cycles was the control arm of the
171 phase 3 study.

172 XELODA in combination with docetaxel was assessed in an open-label, multicenter, randomized trial in
173 75 centers in Europe, North America, South America, Asia, and Australia. A total of 511 patients with
174 metastatic breast cancer resistant to, or recurring during or after an anthracycline-containing therapy, or
175 relapsing during or recurring within two years of completing an anthracycline-containing adjuvant
176 therapy were enrolled. Two hundred and fifty-five (255) patients were randomized to receive
177 XELODA 1250 mg/m² twice daily for 14 days followed by one week without treatment and docetaxel
178 75 mg/m² as a 1 hour intravenous infusion administered in 3 week cycles. In the monotherapy arm, 256
179 patients received docetaxel 100 mg/m² as a 1 hour intravenous infusion administered in 3 week cycles.
180 Patient demographics are provided in Table 4.

XELODA[®] (capecitabine)181
182**Table 4. 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%)

183 ¹Includes 10 patients in combination and 18 patients in monotherapy arms treated with an
184 anthracenedione

XELODA[®] (capecitabine)

185 XELODA in combination with docetaxel resulted in statistically significant improvement in time to
 186 disease progression, overall survival and objective response rate compared to monotherapy with
 187 docetaxel as shown in Table 5 and Figures 2 and 3.

188 **Table 5. 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

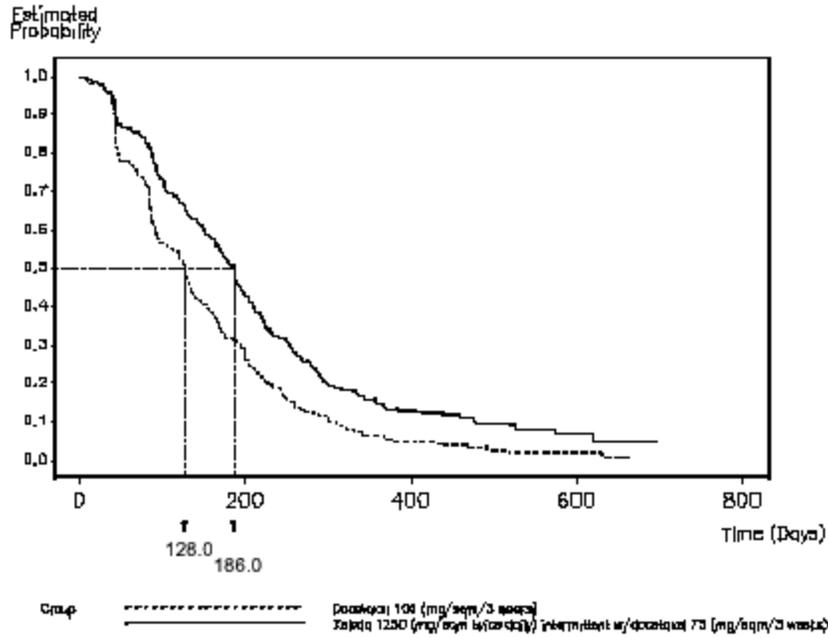
189 ¹ The response rate reported represents a reconciliation of the investigator and IRC assessments
 190 performed by the sponsor according to a predefined algorithm.

191 ² NA = Not Applicable

XELODA® (capecitabine)

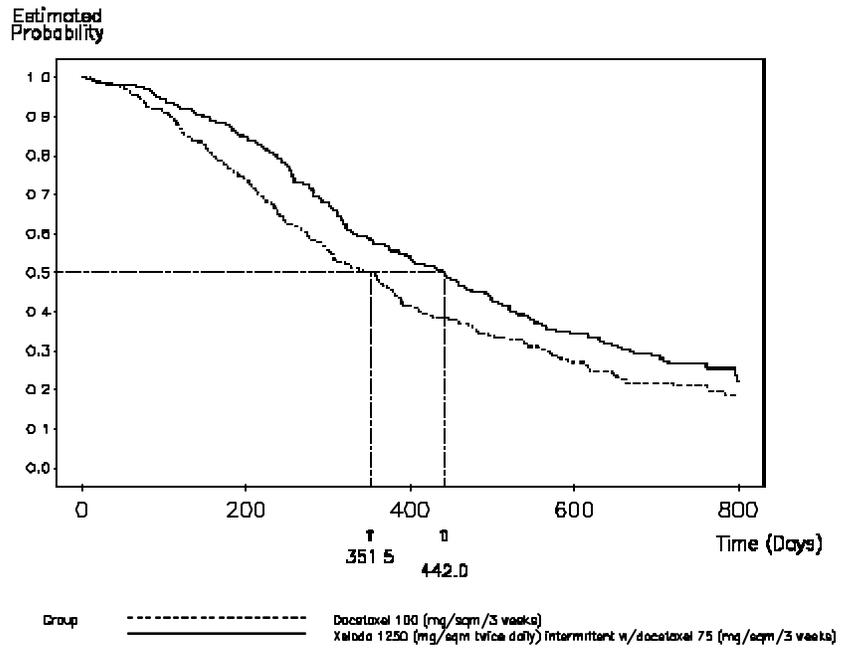
192
193

**Figure 2. Kaplan-Meier Estimates for Time to Disease Progression
XELODA and Docetaxel vs. Docetaxel**



194
195
196

**Figure 3. Kaplan-Meier Estimates of Survival
XELODA and Docetaxel vs. Docetaxel**



197

XELODA[®] (capecitabine)

198 *Breast Cancer Monotherapy:* The antitumor activity of XELODA as a monotherapy was evaluated in
 199 an open-label single-arm trial conducted in 24 centers in the US and Canada. A total of 162 patients
 200 with stage IV breast cancer were enrolled. The primary endpoint was tumor response rate in patients
 201 with measurable disease, with response defined as a $\geq 50\%$ decrease in sum of the products of the
 202 perpendicular diameters of bidimensionally measurable disease for at least 1 month. XELODA was
 203 administered at a dose of 1255 mg/m² twice daily for 2 weeks followed by a 1-week rest period and
 204 given as 3-week cycles. The baseline demographics and clinical characteristics for all patients (n=162)
 205 and those with measurable disease (n=135) are shown in Table 6. Resistance was defined as
 206 progressive disease while on treatment, with or without an initial response, or relapse within 6 months of
 207 completing treatment with an anthracycline-containing adjuvant chemotherapy regimen.
 208

209 **Table 6. Baseline Demographics and Clinical Characteristics**
 210 **Single Arm Breast Cancer Trial**

	Patients With Measurable Disease (n=135)	All Patients (n=162)
Age (median, years)	55	56
Karnofsky PS	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%)

211 ¹Lung, pleura, liver, peritoneum

212 ²Includes 2 patients treated with an anthracenedione

XELODA[®] (capecitabine)

213 Antitumor responses for patients with disease resistant to both paclitaxel and an anthracycline are shown
214 in Table 7.

215 **Table 7. Response Rates in Doubly-Resistant Patients**
216 **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 to 233)

217 ¹Includes 2 patients treated with an anthracenedione

218 ²From date of first response

219 For the subgroup of 43 patients who were doubly resistant, the median time to progression was 102
220 days and the median survival was 255 days. The objective response rate in this population was
221 supported by a response rate of 18.5% (1 CR, 24 PRs) in the overall population of 135 patients with
222 measurable disease, who were less resistant to chemotherapy (see Table 6). The median time to
223 progression was 90 days and the median survival was 306 days.

224 INDICATIONS AND USAGE

225 **Colorectal Cancer:** XELODA is indicated as first-line treatment of patients with metastatic colorectal
226 carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy
227 has shown a survival benefit compared to 5-FU/LV alone. A survival benefit over 5-FU/LV has not
228 been demonstrated with XELODA monotherapy. Use of XELODA instead of 5-FU/LV in
229 combinations has not been adequately studied to assure safety or preservation of the survival advantage.

230 **Breast Cancer Combination Therapy:** XELODA in combination with docetaxel is indicated for the
231 treatment of patients with metastatic breast cancer after failure of prior anthracycline containing
232 chemotherapy.

233 **Breast Cancer Monotherapy:** XELODA monotherapy is also indicated for the treatment of patients
234 with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy
235 regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated, eg,
236 patients who have received cumulative doses of 400 mg/m² of doxorubicin or doxorubicin equivalents.

XELODA[®] (capecitabine)

237 Resistance is defined as progressive disease while on treatment, with or without an initial response, or
238 relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen.

239 CONTRAINDICATIONS

240 XELODA is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil. XELODA
241 is also contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min
242 [Cockcroft and Gault]) (see CLINICAL PHARMACOLOGY: *Special Populations*).

243 WARNINGS

244 **Renal Insufficiency:** Patients with moderate renal impairment at baseline require dose reduction (see
245 DOSAGE AND ADMINISTRATION). Patients with mild and moderate renal impairment at baseline
246 should be carefully monitored for adverse events. Prompt interruption of therapy with subsequent dose
247 adjustments is recommended if a patient develops a grade 2 to 4 adverse event as outlined in Table 14
248 in DOSAGE AND ADMINISTRATION.

249 **Coagulopathy:** See box warning.

250 **Diarrhea:** XELODA can induce diarrhea, sometimes severe. Patients with severe diarrhea should be
251 carefully monitored and given fluid and electrolyte replacement if they become dehydrated. In the overall
252 clinical trial safety database of XELODA monotherapy (N=875), the median time to first occurrence of
253 grade 2 to 4 diarrhea was 34 days (range from 1 to 369 days). The median duration of grade 3 to 4
254 diarrhea was 5 days. National Cancer Institute of Canada (NCIC) grade 2 diarrhea is defined as an
255 increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an increase of 7 to 9 stools/day or
256 incontinence and malabsorption, and grade 4 diarrhea as an increase of ≥ 10 stools/day or grossly
257 bloody diarrhea or the need for parenteral support. If grade 2, 3 or 4 diarrhea occurs, administration of
258 XELODA should be immediately interrupted until the diarrhea resolves or decreases in intensity to
259 grade 1. Following a reoccurrence of grade 2 diarrhea or occurrence of any grade 3 or 4 diarrhea,
260 subsequent doses of XELODA should be decreased (see DOSAGE AND ADMINISTRATION).
261 Standard antidiarrheal treatments (eg, loperamide) are recommended.

262 Necrotizing enterocolitis (typhlitis) has been reported.

263 **Geriatric Patients:** Patients ≥ 80 years old may experience a greater incidence of grade 3 or 4
264 adverse events (see PRECAUTIONS: *Geriatric Use*). In the overall clinical trial safety database of
265 XELODA monotherapy (N=875), 62% of the 21 patients ≥ 80 years of age treated with XELODA
266 experienced a treatment-related grade 3 or 4 adverse event: diarrhea in 6 (28.6%), nausea in 3
267 (14.3%), hand-and-foot syndrome in 3 (14.3%), and vomiting in 2 (9.5%) patients. Among the 10
268 patients 70 years of age and greater (no patients were >80 years of age) treated with XELODA in
269 combination with docetaxel, 30% (3 out of 10) of patients experienced grade 3 or 4 diarrhea and
270 stomatitis, and 40% (4 out of 10) experienced grade 3 hand-and-foot syndrome.

XELODA[®] (capecitabine)

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

276 **Pregnancy:** XELODA may cause fetal harm when given to a pregnant woman. Capecitabine at doses
277 of 198 mg/kg/day during organogenesis caused malformations and embryo death in mice. In separate
278 pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.2 times the
279 corresponding values in patients administered the recommended daily dose. Malformations in mice
280 included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and
281 dilation of cerebral ventricles. At doses of 90 mg/kg/day, capecitabine given to pregnant monkeys
282 during organogenesis caused fetal death. This dose produced 5'-DFUR AUC values about 0.6 times
283 the corresponding values in patients administered the recommended daily dose. There are no adequate
284 and well-controlled studies in pregnant women using XELODA. If the drug is used during pregnancy, or
285 if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential
286 hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant
287 while receiving treatment with XELODA.

288 PRECAUTIONS

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

293 **Combination With Other Drugs:** Use of XELODA in combination with irinotecan has not been
294 adequately studied.

295 **Hand-and-Foot Syndrome:** Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or
296 chemotherapy-induced acral erythema) is a cutaneous toxicity (median time to onset of 79 days, range
297 from 11 to 360 days) with a severity range of grades 1 to 3. Grade 1 is characterized by any of the
298 following: numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or
299 feet and/or discomfort which does not disrupt normal activities. Grade 2 hand-and-foot syndrome is
300 defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the
301 patient's activities of daily living. Grade 3 hand-and-foot syndrome is defined as moist desquamation,
302 ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the
303 patient to be unable to work or perform activities of daily living. If grade 2 or 3 hand-and-foot
304 syndrome occurs, administration of XELODA should be interrupted until the event resolves or
305 decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of
306 XELODA should be decreased (see DOSAGE AND ADMINISTRATION).

XELODA[®] (capecitabine)

307 *Cardiotoxicity:* The cardiotoxicity observed with XELODA includes myocardial infarction/ischemia,
308 angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and
309 cardiomyopathy. These adverse events may be more common in patients with a prior history of
310 coronary artery disease.

311 *Hepatic Insufficiency:* Patients with mild to moderate hepatic dysfunction due to liver metastases
312 should be carefully monitored when XELODA is administered. The effect of severe hepatic dysfunction
313 on the disposition of XELODA is not known (see CLINICAL PHARMACOLOGY and DOSAGE
314 AND ADMINISTRATION).

315 *Hyperbilirubinemia:* In the overall clinical trial safety database of XELODA monotherapy (N=875),
316 grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) and grade 4 (>3 x ULN)
317 hyperbilirubinemia occurred in 3.9% (n=34) of 875 patients with either metastatic breast or colorectal
318 cancer who received at least one dose of XELODA 1250 mg/m² twice daily as monotherapy for 2
319 weeks followed by a 1-week rest period. Of 566 patients who had hepatic metastases at baseline and
320 309 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 22.8%
321 and 12.3%, respectively. Of the 167 patients with grade 3 or 4 hyperbilirubinemia, 18.6% (n=31) also
322 had postbaseline elevations (grades 1 to 4, without elevations at baseline) in alkaline phosphatase and
323 27.5% (n=46) had postbaseline elevations in transaminases at any time (not necessarily concurrent).
324 The majority of these patients, 64.5% (n=20) and 71.7% (n=33), had liver metastases at baseline. In
325 addition, 57.5% (n=96) and 35.3% (n=59) of the 167 patients had elevations (grades 1 to 4) at both
326 pre baseline and post baseline in alkaline phosphatase or transaminases, respectively. Only 7.8%
327 (n=13) and 3.0% (n=5) had grade 3 or 4 elevations in alkaline phosphatase or transaminases.

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

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

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

XELODA[®] (capecitabine)

343 *Hematologic:* In 875 patients with either metastatic breast or colorectal cancer who received a dose of
344 1250 mg/m² administered twice daily as monotherapy for 2 weeks followed by a 1-week rest period,
345 3.2%, 1.7%, and 2.4% of patients had grade 3 or 4 neutropenia, thrombocytopenia or decreases in
346 hemoglobin, respectively. In 251 patients with metastatic breast cancer who received a dose of
347 XELODA in combination with docetaxel, 68% had grade 3 or 4 neutropenia, 2.8% had grade 3 or 4
348 thrombocytopenia, and 9.6% had grade 3 or 4 anemia.

349 ***Carcinogenesis, Mutagenesis and Impairment of Fertility:*** Adequate studies investigating the
350 carcinogenic potential of XELODA have not been conducted. Capecitabine was not mutagenic in vitro
351 to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay).
352 Capecitabine was clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic in vivo
353 to mouse bone marrow (micronucleus test). Fluorouracil causes mutations in bacteria and yeast.
354 Fluorouracil also causes chromosomal abnormalities in the mouse micronucleus test in vivo.

355 ***Impairment of Fertility:*** In studies of fertility and general reproductive performance in mice, oral
356 capecitabine doses of 760 mg/kg/day disturbed estrus and consequently caused a decrease in fertility.
357 In mice that became pregnant, no fetuses survived this dose. The disturbance in estrus was reversible. In
358 males, this dose caused degenerative changes in the testes, including decreases in the number of
359 spermatocytes and spermatids. In separate pharmacokinetic studies, this dose in mice produced 5'-
360 DFUR AUC values about 0.7 times the corresponding values in patients administered the
361 recommended daily dose.

362 ***Information for Patients (see Patient Package Insert):*** Patients and patients' caregivers should be
363 informed of the expected adverse effects of XELODA, particularly nausea, vomiting, diarrhea, and
364 hand-and-foot syndrome, and should be made aware that patient-specific dose adaptations during
365 therapy are expected and necessary (see DOSAGE AND ADMINISTRATION). Patients should be
366 encouraged to recognize the common grade 2 toxicities associated with XELODA treatment.

367 ***Diarrhea:*** Patients experiencing grade 2 diarrhea (an increase of 4 to 6 stools/day or nocturnal stools)
368 or greater should be instructed to stop taking XELODA immediately. Standard antidiarrheal treatments
369 (eg, loperamide) are recommended.

370 ***Nausea:*** Patients experiencing grade 2 nausea (food intake significantly decreased but able to eat
371 intermittently) or greater should be instructed to stop taking XELODA immediately. Initiation of
372 symptomatic treatment is recommended.

373 ***Vomiting:*** Patients experiencing grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater
374 should be instructed to stop taking XELODA immediately. Initiation of symptomatic treatment is
375 recommended.

376 ***Hand-and-Foot Syndrome:*** Patients experiencing grade 2 hand-and-foot syndrome (painful erythema
377 and swelling of the hands and/or feet and/or discomfort affecting the patients' activities of daily living) or
378 greater should be instructed to stop taking XELODA immediately.

XELODA[®] (capecitabine)

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

382 *Fever and Neutropenia:* Patients who develop a fever of 100.5°F or greater or other evidence of
383 potential infection should be instructed to call their physician.

384 ***Drug-Food Interaction:*** In all clinical trials, patients were instructed to administer XELODA within
385 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food,
386 it is recommended that XELODA be administered with food (see DOSAGE AND
387 ADMINISTRATION).

Drug-Drug Interactions:

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

393 *Anticoagulants:* Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant
394 therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with
395 great frequency and the anticoagulant dose should be adjusted accordingly (see BOX WARNINGS
396 and CLINICAL PHARMACOLOGY). Altered coagulation parameters and/or bleeding have been
397 reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as
398 warfarin and phenprocoumon. These events occurred within several days and up to several months after
399 initiating XELODA therapy and, in a few cases, within one month after stopping XELODA. These
400 events occurred in patients with and without liver metastases. In a drug interaction study with single dose
401 warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum
402 observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome
403 P450 2C9 by capecitabine and/or its metabolites (see CLINICAL PHARMACOLOGY.)

404 *CYP2C9 substrates:* Other than warfarin, no formal drug-drug interaction studies between XELODA
405 and other CYP2C9 substrates have been conducted. Care should be exercised when XELODA is co-
406 administered with CYP2C9 substrates.

407 *Phenytoin:* The level of phenytoin should be carefully monitored in patients taking XELODA and
408 phenytoin dose may need to be reduced (see DOSAGE AND ADMINISTRATION: *Dose*
409 *Modification Guidelines*). Postmarketing reports indicate that some patients receiving XELODA and
410 phenytoin had toxicity associated with elevated phenytoin levels. Formal drug-drug interaction studies
411 with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition
412 of the CYP2C9 isoenzyme by capecitabine and/or its metabolites (see PRECAUTIONS: *Drug-Drug*
413 *Interactions: Anticoagulants*).

XELODA[®] (capecitabine)

414 *Leucovorin:* The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by
415 leucovorin. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly
416 patients receiving weekly leucovorin and fluorouracil.

417 *Pregnancy: Teratogenic Effects:* Category D (see WARNINGS). Women of childbearing potential
418 should be advised to avoid becoming pregnant while receiving treatment with XELODA.

419 *Nursing Women:* Lactating mice given a single oral dose of capecitabine excreted significant amounts
420 of capecitabine metabolites into the milk. Because of the potential for serious adverse reactions in
421 nursing infants from capecitabine, it is recommended that nursing be discontinued when receiving
422 XELODA therapy.

423 *Pediatric Use:* The safety and effectiveness of XELODA in persons <18 years of age have not been
424 established.

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

ADVERSE REACTIONS

428 *Colorectal Cancer:* Table 8 shows the adverse events occurring in 5% of patients from pooling the
429 two phase 3 trials in colorectal cancer. Rates are rounded to the nearest whole number. A total of 596
430 patients with metastatic colorectal cancer were treated with 1250 mg/m² twice a day of XELODA
431 administered for 2 weeks followed by a 1-week rest period, and 593 patients were administered 5-FU
432 and leucovorin in the Mayo regimen (20 mg/m² leucovorin IV followed by 425 mg/m² IV bolus 5-FU,
433 on days 1-5, every 28 days). In the pooled colorectal database the median duration of treatment was
434 139 days for capecitabine-treated patients and 140 days for 5-FU/LV-treated patients. A total of 78
435 (13%) and 63 (11%) capecitabine and 5-FU/LV-treated patients, respectively, discontinued treatment
436 because of adverse events/intercurrent illness. A total of 82 deaths due to all causes occurred either on
437 study or within 28 days of receiving study drug: 50 (8.4%) patients randomized to XELODA and 32
438 (5.4%) randomized to 5-FU/LV.

XELODA[®] (capecitabine)

439 **Table 8. Pooled Phase 3 Colorectal Trials:**
 440 **Percent Incidence of Adverse Events Related or Unrelated to Treatment in ³5% of Patients**

	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
<i>Metabolism</i>						
Appetite Decreased	26	3	<1	31	2	<1
Dehydration	7	2	<1	8	3	1

XELODA[®] (capecitabine)

	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>Eye</i>						
Eye Irritation	13	–	–	10	<1	–
Vision Abnormal	5	–	–	2	–	–
<i>Respiratory</i>						
Dyspnea	14	1	–	10	<1	1
Cough	7	<1	1	8	–	–
Pharyngeal Disorder	5	–	–	5	–	–
Epistaxis	3	<1	–	6	–	–
Sore Throat	2	–	–	6	–	–
<i>Musculoskeletal</i>						
Back Pain	10	2	–	9	<1	–
Arthralgia	8	1	–	6	1	–
<i>Vascular</i>						
Venous Thrombosis	8	3	<1	6	2	–
<i>Psychiatric</i>						
Mood Alteration	5	–	–	6	<1	–
Depression	5	–	–	4	<1	–
<i>Infections</i>						
Viral	5	<1	–	5	<1	–
<i>Blood and Lymphatic</i>						
Anemia	80	2	<1	79	1	<1
Neutropenia	13	1	2	46	8	13
<i>Hepatobiliary</i>						
Hyperbilirubinemia	48	18	5	17	3	3

441 – Not observed

442 * Excluding vertigo

443 NA = Not Applicable

444 **Breast Cancer Combination:** The following data are shown for the combination study with
445 XELODA and docetaxel in patients with metastatic breast cancer in Table 9. In the XELODA and
446 docetaxel combination arm the treatment was XELODA administered orally 1250 mg/m² twice daily as
447 intermittent therapy (2 weeks of treatment followed by one week without treatment) for at least 6 weeks
448 and docetaxel administered as a 1 hour intravenous infusion at a dose of 75 mg/m² on the first day of

XELODA[®] (capecitabine)

449 each 3 week cycle for at least 6 weeks. In the monotherapy arm docetaxel was administered as a 1
 450 hour intravenous infusion at a dose of 100 mg/m² on the first day of each 3 week cycle for at least 6
 451 weeks. The mean duration of treatment was 129 days in the combination arm and 98 days in the
 452 monotherapy arm. A total of 66 patients (26%) in the combination arm and 49 (19%) in the
 453 monotherapy arm withdrew from the study because of adverse events. The percentage of patients
 454 requiring dose reductions due to adverse events were 65% in the combination arm and 36% in the
 455 monotherapy arm. The percentage of patients requiring treatment interruptions due to adverse events in
 456 the combination arm was 79%. Treatment interruptions were part of the dose modification scheme for
 457 the combination therapy arm but not for the docetaxel monotherapy treated patients.

458 **Table 9. Percent Incidence of Adverse Events Considered Related or Unrelated to Treatment**
 459 **in [≥]5% of Patients Participating in the**
 460 **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 %
Number of Patients with at least one Adverse Event	99	76.5	29.1	97	57.6	31.8
Body System/Adverse Event						
GI						
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	–	–

XELODA® (capecitabine)

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>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	–	–
<i>General</i>						
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	–	–
<i>Neurological</i>						
Taste disturbance	16	<1	–	14	<1	–
Headache	15	3	–	15	2	–
Paraesthesia	12	<1	–	16	1	–
Dizziness	12	–	–	8	<1	–
Insomnia	8	–	–	10	<1	–
Peripheral Neuropathy	6	–	–	10	1	–
Hypoesthesia	4	<1	–	8	<1	–

XELODA® (capecitabine)

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>Metabolism</i>						
Anorexia	13	1	–	11	<1	–
Appetite Decreased	10	–	–	5	–	–
Weight Decreased	7	–	–	5	–	–
Dehydration	10	2	–	7	<1	<1
<i>Eye</i>						
Lacrimation increased	12	–	–	7	<1	–
Conjunctivitis	5	–	–	4	–	–
Eye Irritation	5	–	–	1	–	–
<i>Musculoskeletal</i>						
Arthralgia	15	2	–	24	3	–
Myalgia	15	2	–	25	2	–
Back pain	12	<1	–	11	3	–
Bone pain	8	<1	–	10	2	–
<i>Cardiac</i>						
Edema	33	<2	–	34	<3	1
<i>Blood</i>						
Neutropenic fever	16	3	13	21	5	16
<i>Respiratory</i>						
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	–
<i>Infection</i>						
Oral Candidiasis	7	<1	–	8	<1	–
Urinary Tract Infection	6	<1	–	4	–	–
Upper Respiratory Tract	4	–	–	5	1	–

XELODA[®] (capecitabine)

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>Vascular</i>						
Flushing	5	–	–	5	–	–
Lymphoedema	3	<1	–	5	1	–
<i>Psychiatric</i>						
Depression	5	–	–	5	1	–

461 – Not observed.

462 NA = Not Applicable

463 **Table 10. Percent of Patients With Laboratory Abnormalities Participating in the**
464 **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 %
Body System/Adverse Event						
<i>Hematologic</i>						
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
<i>Hepatobiliary</i>						
Hyperbilirubinemia	20	7	2	6	2	2

465

466 **Breast Cancer XELODA Monotherapy:** The following data are shown for the study in stage IV
467 breast cancer patients who received a dose of 1250 mg/m² administered twice daily for 2 weeks

XELODA[®] (capecitabine)

468 followed by a 1-week rest period. The mean duration of treatment was 114 days. A total of 13 out of
469 162 patients (8%) discontinued treatment because of adverse events/intercurrent illness.

470 **Table 11. Percent Incidence of Adverse Events Considered Remotely, Possibly or Probably**
471 **Related to Treatment in ³5% of Patients Participating in the Single Arm Trial in Stage IV**
472 **Breast Cancer**

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
	Total	Grade 3	Grade 4
Body System/Adverse Event			
<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>			
Paraesthesia	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	–	–
<i>Cardiac</i>			
Edema	9	1	–

XELODA[®] (capecitabine)

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

473 – Not observed

474 NA = Not Applicable

475 ***OTHER ADVERSE EVENTS:***

476 ***XELODA and Docetaxel in Combination:*** Shown below by body system are the clinically relevant
 477 adverse events in <5% of patients in the overall clinical trial safety database of 251 patients (Study
 478 Details) reported as related to the administration of XELODA in combination with docetaxel and that
 479 were clinically at least remotely relevant. In parentheses is the incidence of grade 3 and 4 occurrences of
 480 each adverse event.

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

483 *Gastrointestinal:* ileus (0.39), necrotizing enterocolitis (0.39), esophageal ulcer (0.39), hemorrhagic
 484 diarrhea (0.80)

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

486 *Cardiac:* supraventricular tachycardia (0.39)

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

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

489 *Vascular:* hypotension (1.20), venous phlebitis & thrombophlebitis (0.39), postural hypotension (0.80)

490 *Renal:* renal failure (0.39)

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

493 *Immune System:* hypersensitivity (1.20)

XELODA[®] (capecitabine)

494 ***XELODA Monotherapy:*** Shown below by body system are the clinically relevant adverse events in
 495 <5% of patients in the overall clinical trial safety database of 875 patients (phase 3 colorectal studies —
 496 596 patients, phase 2 colorectal study — 34 patients, phase 2 breast cancer studies — 245 patients)
 497 reported as related to the administration of XELODA and that were clinically at least remotely relevant.
 498 In parentheses is the incidence of grade 3 or 4 occurrences of each adverse event.

499 *Gastrointestinal:* abdominal distension, dysphagia, proctalgia, ascites (0.1), gastric ulcer (0.1), ileus
 500 (0.3), toxic dilation of intestine, gastroenteritis (0.1)

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

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

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

507 *Metabolism:* increased weight, cachexia (0.4), hypertriglyceridemia (0.1), hypokalemia,
 508 hypomagnesemia

509 *Eye:* conjunctivitis

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

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

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

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

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

518 *Vascular:* hypotension (0.2), hypertension (0.1), lymphoedema (0.1), pulmonary embolism (0.2),
 519 cerebrovascular accident (0.1)

520 *Psychiatric:* depression, confusion (0.1)

521 *Renal:* renal impairment (0.6)

522 *Ear:* vertigo

XELODA® (capecitabine)

523 *Hepatobiliary:* hepatic fibrosis (0.1), hepatitis (0.1), cholestatic hepatitis (0.1), abnormal liver function
524 tests

525 *Immune System:* drug hypersensitivity (0.1)

526 *Postmarketing:* hepatic failure

527 **OVERDOSAGE**

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

534 Single doses of XELODA were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg (2.4,
535 4.8, and 9.6 times the recommended human daily dose on a mg/m² basis).

536 **DOSAGE AND ADMINISTRATION**

537 The recommended dose of XELODA is 1250 mg/m² administered orally twice daily (morning and
538 evening; equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by a 1-week rest period given
539 as 3-week cycles. XELODA tablets should be swallowed with water within 30 minutes after a meal.
540 Table 12 displays the total daily dose by body surface area and the number of tablets to be taken at
541 each dose.

542 **Table 12. 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

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

XELODA[®] (capecitabine)

544 ***Dose Modification Guidelines:*** Patients should be carefully monitored for toxicity. Toxicity due to
 545 XELODA administration may be managed by symptomatic treatment, dose interruptions and
 546 adjustment of XELODA dose. Once the dose has been reduced it should not be increased at a later
 547 time.

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

551 Dose modification for the use of XELODA and docetaxel in combination are shown in Table 13.

552 **Table 13: XELODA in Combination with Docetaxel Dose Reduction Schedule**
 553

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 mg/m ² of docetaxel. Prophylaxis for toxicities should be implemented where possible.	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
2nd appearance of same toxicity	Grade 2 occurring during the 14 days of XELODA treatment: interrupt XELODA treatment until resolved to grade 0-1. Treatment may be	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	Discontinue treatment

XELODA[®] (capecitabine)

Toxicity NCIC grades*	Grade 2	Grade 3	Grade 4
	<p>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>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>	
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. 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</p>	Discontinue treatment.	

XELODA[®] (capecitabine)

Toxicity NCIC grades*	Grade 2	Grade 3	Grade 4
	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.		
4th appearance of same toxicity	Discontinue treatment.		

554 *National Cancer Institute of Canada Common Toxicity Criteria were used except for hand-foot syndrome (see
555 PRECAUTIONS).
556

557 Dose modification for the use of XELODA as monotherapy is shown in Table 14.

558 **Table 14. Recommended Dose Modifications**

Toxicity NCIC Grades*	During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
• <i>Grade 1</i>	Maintain dose level	Maintain dose level
• <i>Grade 2</i>		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance	Interrupt until resolved to grade 0-1	75%
-3rd appearance	Interrupt until resolved to grade 0-1	50%
-4th appearance	Discontinue treatment permanently	
• <i>Grade 3</i>		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance	Interrupt until resolved to grade 0-1	50%
-3rd appearance	Discontinue treatment permanently	

XELODA[®] (capecitabine)

Toxicity NCIC Grades*	During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
• <i>Grade 4</i>		
-1st 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%

559 *National Cancer Institute of Canada Common Toxicity Criteria were used except for the Hand-and-
560 Foot Syndrome (see PRECAUTIONS).

561 Dosage modifications are not recommended for grade 1 events. Therapy with XELODA should be
562 interrupted upon the occurrence of a grade 2 or 3 adverse experience. Once the adverse event has
563 resolved or decreased in intensity to grade 1, then XELODA therapy may be restarted at full dose or as
564 adjusted according to the above table. If a grade 4 experience occurs, therapy should be discontinued
565 or interrupted until resolved or decreased to grade 1, and therapy should be restarted at 50% of the
566 original dose. Doses of XELODA omitted for toxicity are not replaced or restored; instead the patient
567 should resume the planned treatment cycles.

568 ***Adjustment of Starting Dose in Special Populations:***

569 ***Hepatic Impairment:*** In patients with mild to moderate hepatic dysfunction due to liver metastases, no
570 starting dose adjustment is necessary; however, patients should be carefully monitored. Patients with
571 severe hepatic dysfunction have not been studied.

572 ***Renal Impairment:*** No adjustment to the starting dose of XELODA is recommended in patients with
573 mild renal impairment (creatinine clearance = 51-80 mL/min [Cockcroft and Gault, as shown below]). In
574 patients with moderate renal impairment (baseline creatinine clearance = 30-50 mL/min), a dose
575 reduction to 75% of the XELODA starting dose when used as monotherapy or in combination with
576 docetaxel (from 1250 mg/m² to 950 mg/m² twice daily) is recommended (see CLINICAL
577 PHARMACOLOGY: *Special Populations*). Subsequent dose adjustment is recommended as outlined
578 in Table 14 if a patient develops a grade 2 to 4 adverse event (see WARNINGS).

579 Cockcroft and Gault Equation:

$$580 \text{ Creatinine clearance for males} = \frac{(140 - \text{age [yrs]}) (\text{body wt [kg]})}{581 \quad \quad \quad (72) (\text{serum creatinine [mg/dL]})}$$

583 Creatinine clearance for females = 0.85 x male value

XELODA[®] (capecitabine)

584 *Geriatrics:* Physicians should exercise caution in monitoring the effects of XELODA in the elderly.
585 Insufficient data are available to provide a dosage recommendation.

586 **HOW SUPPLIED**

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

588 **150 mg**

589 color: light peach
590 engraving: XELODA on one side, 150 on the other
591 150 mg tablets packaged in bottles of 120 (NDC 0004-1100-51)

592 **500 mg**

593 color: peach
594 engraving: XELODA on one side, 500 on the other
595 500 mg tablets packaged in bottles of 240 (NDC 0004-1101-16)

596 ***Storage Conditions:*** Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F), keep
597 tightly closed. [See USP Controlled Room Temperature]

598 Maalox is a registered trademark of Novartis.
599 Taxotere is a registered trademark of Aventis Pharmaceuticals Products Inc.
600 For full Taxotere prescribing information, please refer to Taxotere Package Insert.

XELODA[®] (capecitabine)

601 ***PATIENT PACKAGE INSERT (text only):***

602 **Patient Information**

603 **XELODA[®] (capecitabine) Tablets**

604 Read this leaflet before you start taking XELODA[®] [zeh-LOE-duh] and each time you renew
605 your prescription. It contains important information. However, this information does not take the
606 place of talking with your doctor. This information cannot cover all possible risks and benefits of
607 XELODA. Your doctor should always be your first choice for detailed information about your
608 medical condition and this medicine.

609 **What is XELODA?**

610 XELODA is a medicine you take by mouth (orally) that is used to treat:

- 611 • cancer of the colon or rectum that has spread to other parts of the body (metastatic
612 colorectal cancer) when fluoropyrimidine therapy alone is preferred. Patients and
613 physicians should note that combination chemotherapy has shown a survival benefit
614 compared to 5-FU/LV alone. A survival benefit over 5-FU/LV has not been
615 demonstrated with XELODA monotherapy.
- 616 • breast cancer that has spread to other parts of the body and has not responded to
617 treatment with certain other medicines. These medicines include paclitaxel (Taxol[®]) and
618 anthracycline-containing therapy such as Adriamycin[®] and doxorubicin.

619 XELODA is changed in the body to the substance 5-fluorouracil. In some patients with colon,
620 rectum or breast cancer, this substance stops cancer cells from growing and decreases the size of
621 the tumor.

622 **Who should not take XELODA?**

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

- 624 • are nursing a baby. Tell your doctor if you are nursing. XELODA may pass to the
625 baby in your milk and harm the baby.
- 626 • are allergic to 5-fluorouracil.

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

- 628 • **take a blood thinner such as warfarin (Coumadin[®]). This is very important**
629 **because XELODA may increase the effect of the blood thinner. If you are**
630 **taking blood thinners and XELODA , your doctor needs to check how fast**

XELODA[®] (capecitabine)

631 **your blood clots more frequently and adjust the dose of the blood thinner;**
 632 **if needed.**

- 633 • take phenytoin (Dilantin[®]). Your doctor needs to test the levels of phenytoin in
 634 your blood more often or change your dose of phenytoin.
- 635 • are pregnant. XELODA may not be right for you.
- 636 • have kidney problems. Your doctor may prescribe a different medicine or reduce
 637 the XELODA dose.
- 638 • have liver problems. You may need to be checked for liver problems while you
 639 take XELODA.
- 640 • take the vitamin folic acid. It may affect how XELODA works.

641 **How should I take XELODA?**

642 Your doctor will prescribe a dose and treatment plan that is right for *you*. Your doctor may want
 643 you to take a combination of 150 mg and 500 mg tablets for each dose. If a combination of
 644 tablets is prescribed, you must correctly identify the tablets. Taking the wrong tablets could cause
 645 an overdose (too much medicine) or underdose (too little medicine). The 150 mg tablets are light
 646 peach in color and have 150 engraved on one side. The 500 mg tablets are peach in color and
 647 have 500 engraved on one side. Your doctor may change the amount of medicine you take during
 648 your treatment. Your doctor may prescribe XELODA Tablets in combination with Taxotere[®] or
 649 docetaxel injection.

- 650 • Take the tablets in the combination prescribed by your doctor for your **morning and**
 651 **evening** doses.
- 652 • Take the tablets **within 30 minutes after the end of a meal** (breakfast and dinner).
- 653 • **Swallow XELODA with water.**
- 654 • If you miss a dose of XELODA, do not take the missed dose at all and do not double the
 655 next one. Instead, continue your regular dosing schedule and check with your doctor.
- 656 • It is recommended that XELODA be taken for 14 days followed by a 7-day rest period (no
 657 drug), given as a 21-day cycle. Your doctor will tell you how many cycles of treatment you
 658 will need.
- 659 • In case of accidental swallowing, or if you suspect that too much medicine has been taken,
 660 contact your doctor or local poison control center or emergency room **right away**.

XELODA[®] (capecitabine)

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

- 662 • Women should not become pregnant while taking XELODA. XELODA may harm your
663 unborn child. Use effective birth control while taking XELODA. Tell your doctor if you
664 become pregnant.
- 665 • Men should practice birth control measures while taking XELODA.
- 666 • Do not breast-feed. XELODA may pass through your milk and harm the baby.

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

668 The most common side effects of XELODA are:

- 669 • diarrhea, nausea, vomiting, stomatitis (sores in mouth and throat), abdominal (stomach area)
670 pain, upset stomach, constipation, loss of appetite, and dehydration (too much water loss
671 from the body). These side effects are more common in patients age 80 and older.
- 672 • hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb,
673 painful, swollen or red), rash, dry, itchy or discolored skin, nail problems, and hair loss.
- 674 • tiredness, weakness, dizziness, headache, fever, pain (including chest, back, joint, and muscle
675 pain), trouble sleeping, and taste problems.

676 These side effects may differ when taking XELODA in combination with Taxotere. Please consult your
677 doctor for possible side effects that may be caused by taking XELODA with Taxotere.

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

679 **Contact your doctor right away** if you have the side effects listed below. Your doctor can help
680 reduce the chance that the side effects will continue or become serious. Your doctor may tell you
681 to decrease the dose or stop XELODA treatment for a while.

682 **Contact your doctor right away if you have:**

- 683 • **Diarrhea:** if you have more than 4 bowel movements each day or any diarrhea at night
- 684 • **Vomiting:** if you vomit more than once in a 24-hour time period
- 685 • **Nausea:** if you lose your appetite, and the amount of food you eat each day is much less than
686 usual
- 687 • **Stomatitis:** if you have pain, redness, swelling or sores in your mouth

XELODA[®] (capecitabine)

688 • **Hand-and-Foot Syndrome:** if you have pain and swelling or redness of your hands or feet
689 that prevents normal activity

690 • **Fever or Infection:** if you have a temperature of 100.5°F or greater, or other signs of
691 infection

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

How should I store and use XELODA?

696 • **Never share XELODA with anyone.**

697 • **XELODA should be stored at normal room temperature (about 65° to 85° F).**

698 • **Keep this and all other medications out of the reach of children.**

699 • **In case of accidental ingestion or if you suspect that more than the prescribed dose
700 of this medication has been taken, contact your doctor or local poison control center
701 or emergency room IMMEDIATELY.**

General advice about prescription medicines:

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

706

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

710

711

712 Adriamycin is a registered trademark of Pharmacia & Upjohn Company.

713 Coumadin is a registered trademark of DuPont Pharma.

714 Dilantin is a registered trademark of Parke-Davis.

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

716 Taxotere is a registered trademark of Aventis Pharmaceuticals Products Inc.

717

718 R_x only

XELODA[®] (capecitabine)



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

719

720 XXXXXXXXX-XXXX

721 Revised: XXXXX 2001

722 Printed in USA

723 Copyright © 1999-2001 by Roche Laboratories Inc. All rights reserved.