

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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Final Printed Labeling



XELODA®
(capecitabine)
TABLETS

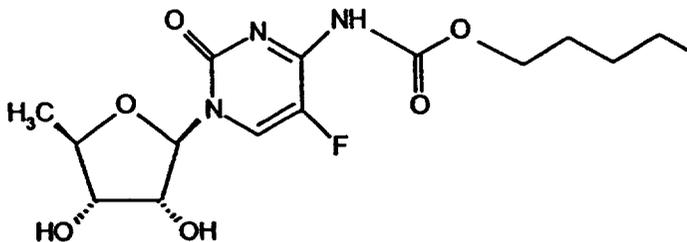
WARNING

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-[(pentylloxy) 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.

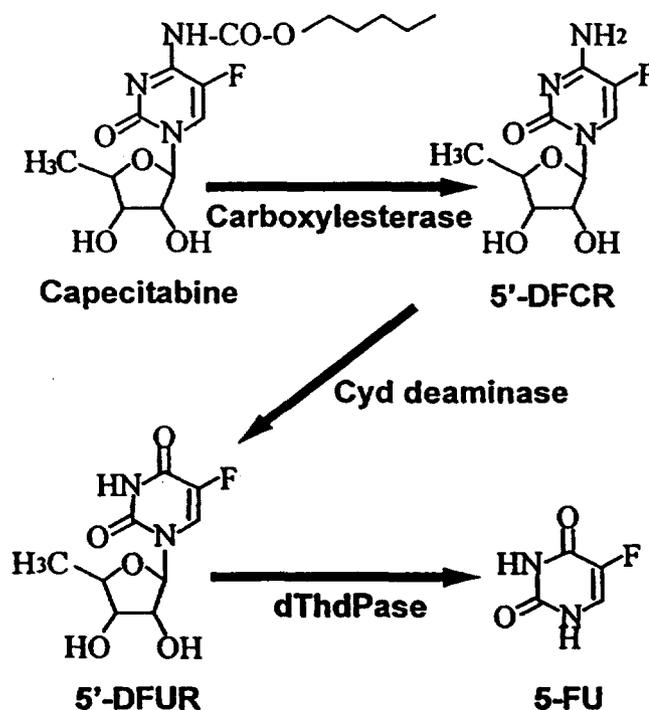
XELODA® (capecitabine)

15 XELODA is supplied as biconvex, oblong film-coated tablets for oral administration. Each light
 16 peach-colored tablet contains 150 mg capecitabine and each peach-colored tablet contains
 17 500 mg capecitabine. The inactive ingredients in XELODA include: anhydrous lactose,
 18 croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium
 19 stearate and purified water. The peach or light peach film coating contains hydroxypropyl
 20 methylcellulose, talc, titanium dioxide, and synthetic yellow and red iron oxides.

21 CLINICAL PHARMACOLOGY

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

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

31 Metabolic Pathway of capecitabine to 5-FU

32

33 **Mechanism of Action:** Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-
 34 deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These

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35 metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor,
36 N⁵-metylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound
37 ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate.
38 Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the
39 synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second,
40 nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine
41 triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA
42 processing and protein synthesis.

43 **Pharmacokinetics in Colorectal Tumors and Adjacent Healthy Tissue:** Following oral
44 administration of XELODA 7 days before surgery in patients with colorectal cancer, the median
45 ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 2.9 (range from 0.9 to
46 8.0). These ratios have not been evaluated in breast cancer patients or compared to 5-FU
47 infusion.

48 **Human Pharmacokinetics:** The pharmacokinetics of XELODA and its metabolites have been
49 evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m²/day. Over this
50 range, the pharmacokinetics of XELODA and its metabolite, 5'-DFCR were dose proportional
51 and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were
52 greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14
53 than on day 1. The elimination half-life of both parent capecitabine and 5-FU was about ¼ of an
54 hour. The inter-patient variability in the C_{max} and AUC of 5-FU was greater than 85%.

55 **Absorption, Distribution, Metabolism and Excretion:** Capecitabine reached peak blood levels in
56 about 1.5 hours (T_{max}) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced
57 both the rate and extent of absorption of capecitabine with mean C_{max} and AUC_{0-∞} decreased by
58 60% and 35%, respectively. The C_{max} and AUC_{0-∞} of 5-FU were also reduced by food by 43%
59 and 21%, respectively. Food delayed T_{max} of both parent and 5-FU by 1.5 hours (see
60 PRECAUTIONS and DOSAGE AND ADMINISTRATION).

61 Plasma protein binding of capecitabine and its metabolites is less than 60% and is not
62 concentration-dependent. Capecitabine was primarily bound to human albumin (approximately
63 35%).

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

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

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73 A clinical phase I study evaluating the effect of XELODA on the pharmacokinetics of docetaxel
74 (Taxotere®) and the effect of docetaxel on the pharmacokinetics of XELODA was conducted in
75 26 patients with solid tumors. XELODA was found to have no effect on the pharmacokinetics of
76 docetaxel (C_{max} and AUC) and docetaxel has no effect on the pharmacokinetics of capecitabine
77 and the 5-FU precursor 5'-DFUR.

78 *Special Populations:*

79 A population analysis of pooled data from the two large controlled studies in patients with
80 colorectal cancer (n=505) who were administered XELODA at 1250 mg/m² twice a day
81 indicated that gender (202 females and 303 males) and race (455 white/caucasian patients,
82 22 black patients, and 28 patients of other race) have no influence on the pharmacokinetics
83 of 5'-DFUR, 5-FU and FBAL. Age has no significant influence on the pharmacokinetics of
84 5'-DFUR and 5-FU over the range of 27 to 86 years. A 20% increase in age results in a
85 15% increase in AUC of FBAL (see WARNINGS and DOSAGE AND
86 ADMINISTRATION).

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

95 ***Renal Insufficiency:*** Following oral administration of 1250 mg/m² capecitabine twice a day
96 to cancer patients with varying degrees of renal impairment, patients with moderate
97 (creatinine clearance = 30-50 mL/min) and severe (creatinine clearance <30 mL/min) renal
98 impairment showed 85% and 258% higher systemic exposure to FBAL on day 1 compared
99 to normal renal function patients (creatinine clearance >80 mL/min). Systemic exposure to
100 5'-DFUR was 42% and 71% greater in moderately and severely renal impaired patients,
101 respectively, than in normal patients. Systemic exposure to capecitabine was about 25%
102 greater in both moderately and severely renal impaired patients (see
103 CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION).

104 *Drug-Drug Interactions:*

105 ***Anticoagulants:*** In four patients with cancer, chronic administration of capecitabine (1250 mg/
106 m² bid) with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and
107 decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by
108 2.8 fold, and the maximum observed mean INR value was increased by 91% (see Box
109 WARNINGS and PRECAUTIONS: *Drug-Drug Interactions*).

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

114 *Antacid:* When Maalox® (20 mL), an aluminum hydroxide- and magnesium hydroxide-
 115 containing antacid, was administered immediately after XELODA (1250 mg/m², n=12 cancer
 116 patients), AUC and C_{max} increased by 16% and 35%, respectively, for capecitabine and by 18%
 117 and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites
 118 (5'-DFUR, 5-FU, FBAL) of XELODA.

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

120 **CLINICAL STUDIES**

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

132 Data from 2 open-label, multicenter, randomized, controlled clinical trials involving 1207
 133 patients support the use of XELODA in the first-line treatment of patients with metastatic
 134 colorectal carcinoma. The two clinical studies were identical in design and were conducted
 135 in 120 centers in different countries. Study 1 was conducted in the US, Canada, Mexico,
 136 and Brazil; Study 2 was conducted in Europe, Israel, Australia, New Zealand, and Taiwan.
 137 Altogether, in both trials, 603 patients were randomized to treatment with XELODA at a
 138 dose of 1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period and given as
 139 3-week cycles; 604 patients were randomized to treatment with 5-FU and leucovorin (20
 140 mg/m² leucovorin IV followed by 425 mg/m² IV bolus 5-FU, on days 1 to 5, every 28
 141 days).

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

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

149 **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)

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

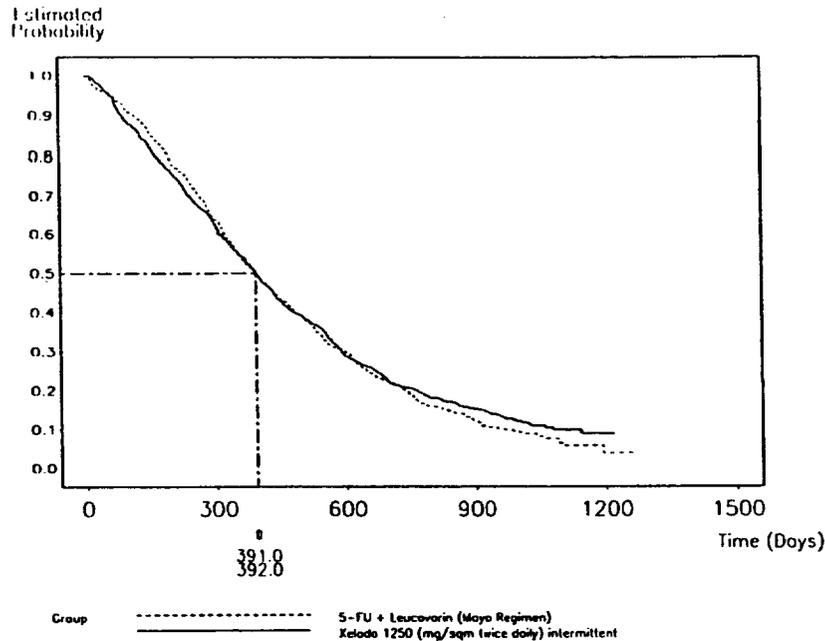
151 **Table 2. Efficacy of XELODA vs. 5-FU/LV in Colorectal Cancer**
 152 **(Study 1)**

	XELODA (n=302)	5-FU/LV (n=303)
Overall Response Rate (% , 95% C.I.)	21 (16-26)	11 (8-15)
(p-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	

153 **Table 3. Efficacy of XELODA vs. 5-FU/LV in Colorectal Cancer**
 154 **(Study 2)**

	XELODA (n=301)	5-FU/LV (n=301)
Overall Response Rate (% , 95% C.I.)	21 (16-26)	14 (10-18)
(p-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	

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

156

157 XELODA was superior to 5-FU/LV for objective response rate in Study 1 and Study 2. The
 158 similarity of XELODA and 5-FU/LV in these studies was assessed by examining the potential
 159 difference between the two treatments. In order to assure that XELODA has a clinically
 160 meaningful survival effect, statistical analyses were performed to determine the percent of the
 161 survival effect of 5-FU/LV that was retained by XELODA. The estimate of the survival effect of
 162 5-FU/LV was derived from a meta-analysis of ten randomized studies from the published
 163 literature comparing 5-FU to regimens of 5-FU/LV that were similar to the control arms used in
 164 these Studies 1 and 2. The method for comparing the treatments was to examine the worst case
 165 (95% confidence upper bound) for the difference between 5-FU/LV and XELODA, and to show
 166 that loss of more than 50% of the 5-FU/LV survival effect was ruled out. It was demonstrated
 167 that the percent of the survival effect of 5-FU/LV maintained was at least 61% for Study 2 and
 168 10% for Study 1. The pooled result is consistent with a retention of at least 50% of the effect of
 169 5-FU/LV. It should be noted that these values for preserved effect are based on the upper bound
 170 of the 5-FU/LV vs. XELODA difference. These results do not exclude the possibility of true
 171 equivalence of XELODA to 5-FU/LV (see Tables 2 and 3 and Kaplan-Meier Figure 1).

172 **Breast Carcinoma:** XELODA has been evaluated in clinical trials in combination with docetaxel
 173 (Taxotere®) and as monotherapy.

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

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

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

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193

**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 (median, years)</i>	52	51
<i>Karnofsky PS (median)</i>	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%)

194 ¹Includes 10 patients in combination and 18 patients in monotherapy arms treated with an
195 anthracenedione

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

199 **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

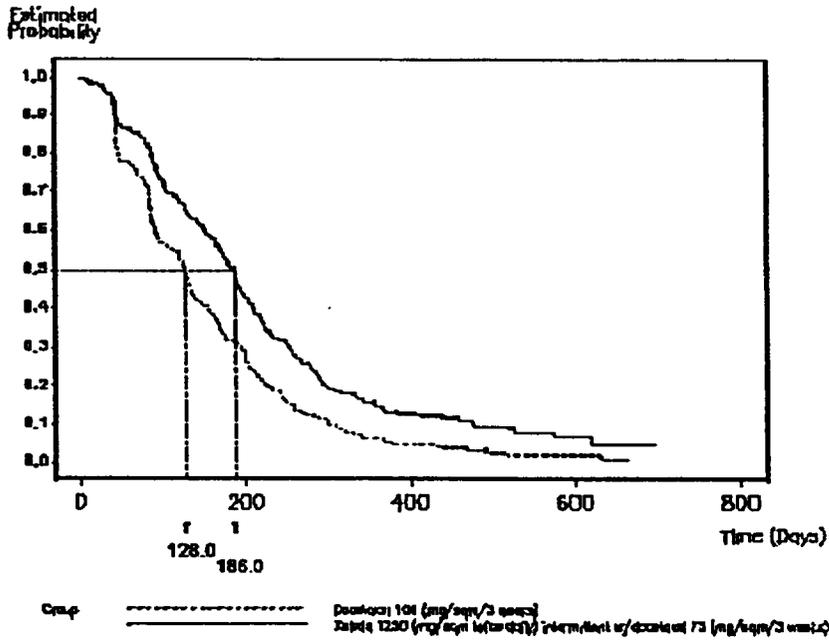
200 ¹ The response rate reported represents a reconciliation of the investigator and IRC assessments
 201 performed by the sponsor according to a predefined algorithm.

202 ² NA = Not Applicable

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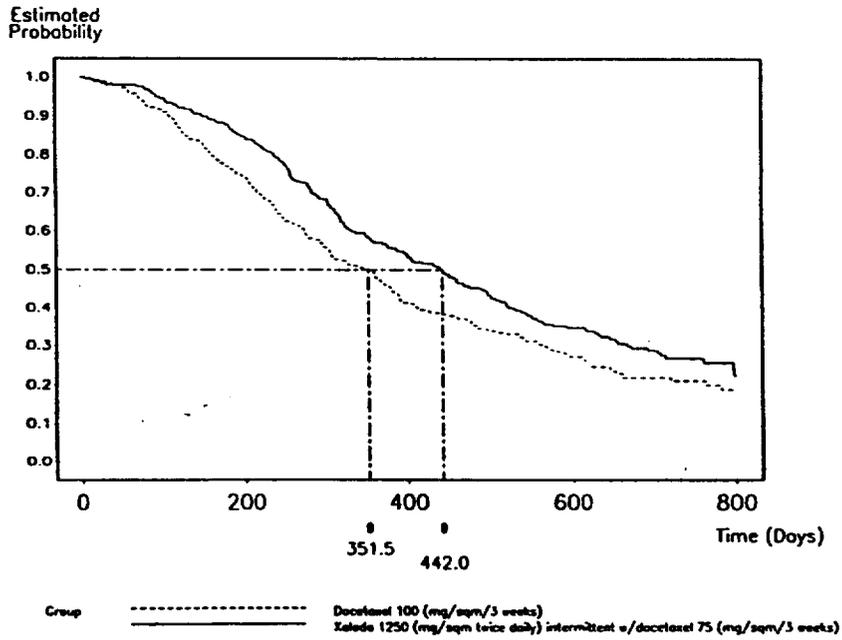
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**Figure 2. Kaplan-Meier Estimates for Time to Disease Progression
XELODA and Docetaxel vs. Docetaxel**



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206
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**Figure 3. Kaplan-Meier Estimates of Survival
XELODA and Docetaxel vs. Docetaxel**



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209 *Breast Cancer Monotherapy:* The antitumor activity of XELODA as a monotherapy was
 210 evaluated in an open-label single-arm trial conducted in 24 centers in the US and Canada. A total
 211 of 162 patients with stage IV breast cancer were enrolled. The primary endpoint was tumor
 212 response rate in patients with measurable disease, with response defined as a $\geq 50\%$ decrease in
 213 sum of the products of the perpendicular diameters of bidimensionally measurable disease for at
 214 least 1 month. XELODA was administered at a dose of 1255 mg/m² twice daily for 2 weeks
 215 followed by a 1-week rest period and given as 3-week cycles. The baseline demographics and
 216 clinical characteristics for all patients (n=162) and those with measurable disease (n=135) are
 217 shown in Table 6. Resistance was defined as progressive disease while on treatment, with or
 218 without an initial response, or relapse within 6 months of completing treatment with an
 219 anthracycline-containing adjuvant chemotherapy regimen.
 220

221 **Table 6. Baseline Demographics and Clinical Characteristics**
 222 **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%)

223 ¹Lung, pleura, liver, peritoneum

224 ²Includes 2 patients treated with an anthracenedione

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

227 **Table 7. Response Rates in Doubly-Resistant Patients**
 228 **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)

229 ¹Includes 2 patients treated with an anthracenedione

230 ²From date of first response

231 For the subgroup of 43 patients who were doubly resistant, the median time to progression was
 232 102 days and the median survival was 255 days. The objective response rate in this population
 233 was supported by a response rate of 18.5% (1 CR, 24 PRs) in the overall population of 135
 234 patients with measurable disease, who were less resistant to chemotherapy (see Table 6). The
 235 median time to progression was 90 days and the median survival was 306 days.

236 **INDICATIONS AND USAGE**

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

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

246 **Breast Cancer Monotherapy:** XELODA monotherapy is also indicated for the treatment of
 247 patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing
 248 chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is
 249 not indicated, eg, patients who have received cumulative doses of 400 mg/m² of doxorubicin or
 250 doxorubicin equivalents. Resistance is defined as progressive disease while on treatment, with or

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251 without an initial response, or relapse within 6 months of completing treatment with an
252 anthracycline-containing adjuvant regimen.

253 CONTRAINDICATIONS

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

258 WARNINGS

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

264 **Diarrhea:** XELODA can induce diarrhea, sometimes severe. Patients with severe diarrhea should
265 be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. In
266 the overall clinical trial safety database of XELODA monotherapy (N=875), the median time to
267 first occurrence of grade 2 to 4 diarrhea was 34 days (range from 1 to 369 days). The median
268 duration of grade 3 to 4 diarrhea was 5 days. National Cancer Institute of Canada (NCIC) grade 2
269 diarrhea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an
270 increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an
271 increase of ≥ 10 stools/day or grossly bloody diarrhea or the need for parenteral support. If grade
272 2, 3 or 4 diarrhea occurs, administration of XELODA should be immediately interrupted until the
273 diarrhea resolves or decreases in intensity to grade 1. Following a reoccurrence of grade 2
274 diarrhea or occurrence of any grade 3 or 4 diarrhea, subsequent doses of XELODA should be
275 decreased (see DOSAGE AND ADMINISTRATION). Standard antidiarrheal treatments (eg,
276 loperamide) are recommended.

277 Necrotizing enterocolitis (typhlitis) has been reported.

278 **Geriatric Patients:** Patients ≥ 80 years old may experience a greater incidence of grade 3 or 4
279 adverse events (see PRECAUTIONS: *Geriatric Use*). In the overall clinical trial safety database
280 of XELODA monotherapy (N=875), 62% of the 21 patients ≥ 80 years of age treated with
281 XELODA experienced a treatment-related grade 3 or 4 adverse event: diarrhea in 6 (28.6%),
282 nausea in 3 (14.3%), hand-and-foot syndrome in 3 (14.3%), and vomiting in 2 (9.5%) patients.
283 Among the 10 patients 70 years of age and greater (no patients were >80 years of age) treated
284 with XELODA in combination with docetaxel, 30% (3 out of 10) of patients experienced grade
285 3 or 4 diarrhea and stomatitis, and 40% (4 out of 10) experienced grade 3 hand-and-foot
286 syndrome.

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

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

305 PRECAUTIONS

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

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

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

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324 hand-and-foot syndrome, subsequent doses of XELODA should be decreased (see DOSAGE
325 AND ADMINISTRATION).

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

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

334 *Hyperbilirubinemia:* In the overall clinical trial safety database of XELODA monotherapy
335 (N=875), grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) and grade 4 (>3
336 x ULN) hyperbilirubinemia occurred in 3.9% (n=34) of 875 patients with either metastatic breast
337 or colorectal cancer who received at least one dose of XELODA 1250 mg/m² twice daily as
338 monotherapy for 2 weeks followed by a 1-week rest period. Of 566 patients who had hepatic
339 metastases at baseline and 309 patients without hepatic metastases at baseline, grade 3 or 4
340 hyperbilirubinemia occurred in 22.8% and 12.3%, respectively. Of the 167 patients with grade 3
341 or 4 hyperbilirubinemia, 18.6% (n=31) also had postbaseline elevations (grades 1 to 4, without
342 elevations at baseline) in alkaline phosphatase and 27.5% (n=46) had postbaseline elevations in
343 transaminases at any time (not necessarily concurrent). The majority of these patients, 64.5%
344 (n=20) and 71.7% (n=33), had liver metastases at baseline. In addition, 57.5% (n=96) and 35.3%
345 (n=59) of the 167 patients had elevations (grades 1 to 4) at both pre baseline and post baseline in
346 alkaline phosphatase or transaminases, respectively. Only 7.8% (n=13) and 3.0% (n=5) had grade
347 3 or 4 elevations in alkaline phosphatase or transaminases.

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

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

358 If drug related grade 2 to 4 elevations in bilirubin occur, administration of XELODA should be
359 immediately interrupted until the hyperbilirubinemia resolves or decreases in intensity to grade 1.
360 NCIC grade 2 hyperbilirubinemia is defined as 1.5 x normal, grade 3 hyperbilirubinemia as 1.5-3

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361 x normal and grade 4 hyperbilirubinemia as >3 x normal. (See recommended dose modifications
362 under DOSAGE AND ADMINISTRATION.)

363 *Hematologic:* In 875 patients with either metastatic breast or colorectal cancer who received a
364 dose of 1250 mg/m² administered twice daily as monotherapy for 2 weeks followed by a 1-week
365 rest period, 3.2%, 1.7%, and 2.4% of patients had grade 3 or 4 neutropenia, thrombocytopenia or
366 decreases in hemoglobin, respectively. In 251 patients with metastatic breast cancer who
367 received a dose of XELODA in combination with docetaxel, 68% had grade 3 or 4 neutropenia,
368 2.8% had grade 3 or 4 thrombocytopenia, and 9.6% had grade 3 or 4 anemia.

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

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

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

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

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

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

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

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

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

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

411 *Drug-Drug Interactions:*

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

416 *Anticoagulants:* Patients receiving concomitant capecitabine and oral coumarin-derivative
417 anticoagulant therapy should have their anticoagulant response (INR or prothrombin time)
418 monitored closely with great frequency and the anticoagulant dose should be adjusted
419 accordingly (see BOX WARNINGS and CLINICAL PHARMACOLOGY). Altered coagulation
420 parameters and/or bleeding have been reported in patients taking XELODA concomitantly with
421 coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred
422 within several days and up to several months after initiating XELODA therapy and, in a few
423 cases, within one month after stopping XELODA. These events occurred in patients with and
424 without liver metastases. In a drug interaction study with single dose warfarin administration,
425 there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR
426 value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450
427 2C9 by capecitabine and/or its metabolites (see CLINICAL PHARMACOLOGY.)

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

431 *Phenytoin:* The level of phenytoin should be carefully monitored in patients taking XELODA
432 and phenytoin dose may need to be reduced (see DOSAGE AND ADMINISTRATION: *Dose*
433 *Modification Guidelines*). Postmarketing reports indicate that some patients receiving XELODA

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434 and phenytoin had toxicity associated with elevated phenytoin levels. Formal drug-drug
435 interaction studies with phenytoin have not been conducted, but the mechanism of interaction is
436 presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine and/or its metabolites (see
437 PRECAUTIONS: *Drug-Drug Interactions: Anticoagulants*).

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

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

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

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

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

452 ADVERSE REACTIONS

453 *Colorectal Cancer:* Table 8 shows the adverse events occurring in $\geq 5\%$ of patients from pooling
454 the two phase 3 trials in colorectal cancer. Rates are rounded to the nearest whole number. A
455 total of 596 patients with metastatic colorectal cancer were treated with 1250 mg/m² twice a day
456 of XELODA administered for 2 weeks followed by a 1-week rest period, and 593 patients were
457 administered 5-FU and leucovorin in the Mayo regimen (20 mg/m² leucovorin IV followed by
458 425 mg/m² IV bolus 5-FU, on days 1-5, every 28 days). In the pooled colorectal database the
459 median duration of treatment was 139 days for capecitabine-treated patients and 140 days for 5-
460 FU/LV-treated patients. A total of 78 (13%) and 63 (11%) capecitabine and 5-FU/LV-treated
461 patients, respectively, discontinued treatment because of adverse events/intercurrent illness. A
462 total of 82 deaths due to all causes occurred either on study or within 28 days of receiving study
463 drug: 50 (8.4%) patients randomized to XELODA and 32 (5.4%) randomized to 5-FU/LV.

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**Table 8. Pooled Phase 3 Colorectal Trials:
Percent Incidence of Adverse Events Related or Unrelated to Treatment in ≥5% 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

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	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

466 – Not observed

467 * Excluding vertigo

468 NA = Not Applicable

469 **Breast Cancer Combination:** The following data are shown for the combination study with
470 XELODA and docetaxel in patients with metastatic breast cancer in Table 9. In the XELODA
471 and docetaxel combination arm the treatment was XELODA administered orally 1250 mg/m²
472 twice daily as intermittent therapy (2 weeks of treatment followed by one week without
473 treatment) for at least 6 weeks and docetaxel administered as a 1 hour intravenous infusion at a
474 dose of 75 mg/m² on the first day of each 3 week cycle for at least 6 weeks. In the monotherapy
475 arm docetaxel was administered as a 1 hour intravenous infusion at a dose of 100 mg/m² on the

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476 first day of each 3 week cycle for at least 6 weeks. The mean duration of treatment was 129 days
 477 in the combination arm and 98 days in the monotherapy arm. A total of 66 patients (26%) in the
 478 combination arm and 49 (19%) in the monotherapy arm withdrew from the study because of
 479 adverse events. The percentage of patients requiring dose reductions due to adverse events were
 480 65% in the combination arm and 36% in the monotherapy arm. The percentage of patients
 481 requiring treatment interruptions due to adverse events in the combination arm was 79%.
 482 Treatment interruptions were part of the dose modification scheme for the combination therapy
 483 arm but not for the docetaxel monotherapy treated patients.

484 **Table 9. Percent Incidence of Adverse Events Considered Related or Unrelated to**
 485 **Treatment in ≥5% of Patients Participating in the**
 486 **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						
<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	-	-

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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>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	–
Hypoaesthesia	4	<1	–	8	<1	–
<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	–	–

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

487 – Not observed.

488 NA = Not Applicable

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489
490**Table 10. 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

491

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

496 **Table 11. Percent Incidence of Adverse Events Considered Remotely, Possibly or Probably**
 497 **Related to Treatment in ≥5% of Patients Participating in the Single Arm Trial in Stage IV**
 498 **Breast Cancer**

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
	Total	Grade 3	Grade 4
GI			
Diarrhea	57	12	3
Nausea	53	4	—
Vomiting	37	4	—
Stomatitis	24	7	—
Abdominal Pain	20	4	—
Constipation	15	1	—
Dyspepsia	8	—	—
Skin and Subcutaneous			
Hand-and-Foot Syndrome	57	11	NA
Dermatitis	37	1	—
Nail Disorder	7	—	—

XELODA® (capecitabine)

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
	Total	Grade 3	Grade 4
General			
Fatigue	41	8	—
Pyrexia	12	1	—
Pain in Limb	6	1	—
Neurological			
Paraesthesia	21	1	—
Headache	9	1	—
Dizziness	8	—	—
Insomnia	8	—	—
Metabolism			
Anorexia	23	3	—
Dehydration	7	4	1
Eye			
Eye Irritation	15	—	—
Musculoskeletal			
Myalgia	9	—	—
Cardiac			
Edema	9	1	—
Blood			
Neutropenia	26	2	2
Thrombocytopenia	24	3	1
Anemia	72	3	1
Lymphopenia	94	44	15
Hepatobiliary			
Hyperbilirubinemia	22	9	2

499 — Not observed

500 NA = Not Applicable

501 **OTHER ADVERSE EVENTS:**

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

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

509 **Gastrointestinal:** ileus (0.39), necrotizing enterocolitis (0.39), esophageal ulcer (0.39),
510 hemorrhagic diarrhea (0.80)

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- 511 *Neurological*: ataxia (0.39), syncope (1.20), taste loss (0.80), polyneuropathy (0.39), migraine
512 (0.39)
- 513 *Cardiac*: supraventricular tachycardia (0.39)
- 514 *Infection*: neutropenic sepsis (2.39), sepsis (0.39), bronchopneumonia (0.39)
- 515 *Blood and Lymphatic*: agranulocytosis (0.39), prothrombin decreased (0.39)
- 516 *Vascular*: hypotension (1.20), venous phlebitis & thrombophlebitis (0.39), postural hypotension
517 (0.80)
- 518 *Renal*: renal failure (0.39)
- 519 *Hepatobiliary*: jaundice (0.39), abnormal liver function tests (0.39), hepatic failure (0.39),
520 hepatic coma (0.39), hepatotoxicity (0.39)
- 521 *Immune System*: hypersensitivity (1.20)
- 522 ***XELODA Monotherapy***: Shown below by body system are the clinically relevant adverse events
523 in <5% of patients in the overall clinical trial safety database of 875 patients (phase 3 colorectal
524 studies — 596 patients, phase 2 colorectal study — 34 patients, phase 2 breast cancer studies —
525 245 patients) reported as related to the administration of XELODA and that were clinically at
526 least remotely relevant. In parentheses is the incidence of grade 3 or 4 occurrences of each
527 adverse event.
- 528 *Gastrointestinal*: abdominal distension, dysphagia, proctalgia, ascites (0.1), gastric ulcer (0.1),
529 ileus (0.3), toxic dilation of intestine, gastroenteritis (0.1)
- 530 *Skin and Subcutaneous*: nail disorder (0.1), sweating increased (0.1), photosensitivity reaction
531 (0.1), skin ulceration, pruritus, radiation recall syndrome (0.2)
- 532 *General*: chest pain (0.2), influenza-like illness, hot flushes, pain (0.1), hoarseness, irritability,
533 difficulty in walking, thirst, chest mass, collapse, fibrosis (0.1), hemorrhage, edema, sedation
- 534 *Neurological*: insomnia, ataxia (0.5), tremor, dysphasia, encephalopathy (0.1), abnormal
535 coordination, dysarthria, loss of consciousness (0.2), impaired balance
- 536 *Metabolism*: increased weight, cachexia (0.4), hypertriglyceridemia (0.1), hypokalemia,
537 hypomagnesemia
- 538 *Eye*: conjunctivitis
- 539 *Respiratory*: cough (0.1), epistaxis (0.1), asthma (0.2), hemoptysis, respiratory distress (0.1),
540 dyspnea

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- 541 *Cardiac:* tachycardia (0.1), bradycardia, atrial fibrillation, ventricular extrasystoles,
542 extrasystoles, myocarditis (0.1), pericardial effusion
- 543 *Infections:* laryngitis (1.0), bronchitis (0.2), pneumonia (0.2), bronchopneumonia (0.2),
544 keratoconjunctivitis, sepsis (0.3), fungal infections (including candidiasis) (0.2)
- 545 *Musculoskeletal:* myalgia, bone pain (0.1), arthritis (0.1), muscle weakness
- 546 *Blood and Lymphatic:* leukopenia (0.2), coagulation disorder (0.1), bone marrow depression
547 (0.1), idiopathic thrombocytopenia purpura (1.0), pancytopenia (0.1)
- 548 *Vascular:* hypotension (0.2), hypertension (0.1), lymphoedema (0.1), pulmonary embolism (0.2),
549 cerebrovascular accident (0.1)
- 550 *Psychiatric:* depression, confusion (0.1)
- 551 *Renal:* renal impairment (0.6)
- 552 *Ear:* vertigo
- 553 *Hepatobiliary:* hepatic fibrosis (0.1), hepatitis (0.1), cholestatic hepatitis (0.1), abnormal liver
554 function tests
- 555 *Immune System:* drug hypersensitivity (0.1)
- 556 *Postmarketing:* hepatic failure

557 OVERDOSAGE

558 The manifestations of acute overdose would include nausea, vomiting, diarrhea, gastrointestinal
559 irritation and bleeding, and bone marrow depression. Medical management of overdose should
560 include customary supportive medical interventions aimed at correcting the presenting clinical
561 manifestations. Although no clinical experience using dialysis as a treatment for XELODA
562 overdose has been reported, dialysis may be of benefit in reducing circulating concentrations of
563 5'-DFUR, a low-molecular weight metabolite of the parent compound.

564 Single doses of XELODA were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg
565 (2.4, 4.8, and 9.6 times the recommended human daily dose on a mg/m² basis).

566 DOSAGE AND ADMINISTRATION

567 The recommended dose of XELODA is 1250 mg/m² administered orally twice daily (morning
568 and evening; equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by a 1-week rest
569 period given as 3-week cycles. XELODA tablets should be swallowed with water within 30

XELODA® (capecitabine)

570 minutes after a meal. Table 12 displays the total daily dose by body surface area and the number
571 of tablets to be taken at each dose.

572 **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

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

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

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

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

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

583

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	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	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

XELODA® (capecitabine)

Toxicity NCIC grades*	Grade 2	Grade 3	Grade 4
	<p>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, then continue at 100% of the original XELODA and docetaxel dose. Prophylaxis for toxicities should be implemented where possible.</p>	<p>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 75% of the original XELODA dose and at 55 mg/m² of docetaxel. Prophylaxis for toxicities should be implemented where possible.</p>	
<p>2nd appearance of same toxicity</p>	<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</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>	<p>Discontinue treatment</p>

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Toxicity NCIC grades*	Grade 2	Grade 3	Grade 4
	toxicities should be implemented where possible.		
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 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.	
4th appearance of same toxicity	Discontinue treatment.		

584 *National Cancer Institute of Canada Common Toxicity Criteria were used except for hand-foot syndrome (see
585 PRECAUTIONS).
586

XELODA® (capecitabine)

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

588 **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	
• <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%

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

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

XELODA® (capecitabine)**598 Adjustment of Starting Dose in Special Populations:**

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

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

610 Cockcroft and Gault Equation:

$$611 \qquad \qquad \qquad \qquad \qquad \qquad \qquad (140 - \text{age [yrs]}) (\text{body wt [kg]})$$

$$612 \quad \text{Creatinine clearance for males} = \frac{\qquad \qquad \qquad \qquad \qquad \qquad \qquad}{\qquad \qquad \qquad \qquad \qquad \qquad \qquad}$$

$$613 \qquad \qquad \qquad \qquad \qquad \qquad \qquad (72) (\text{serum creatinine [mg/dL]})$$

614 Creatinine clearance for females = 0.85 x male value

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

617 HOW SUPPLIED

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

619 150 mg

620 color: light peach

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

622 150 mg tablets packaged in bottles of 120 (NDC 0004-1100-51)

623 500 mg

624 color: peach

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

626 500 mg tablets packaged in bottles of 240 (NDC 0004-1101-16)

XELODA® (capecitabine)

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

629 Maalox is a registered trademark of Novartis.

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

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

XELODA® (capecitabine)

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

633 **Patient Information**

634 **XELODA® (capecitabine) Tablets**

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

640 **What is XELODA?**

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

- 642 • cancer of the colon or rectum that has spread to other parts of the body (metastatic
643 colorectal cancer) when fluoropyrimidine therapy alone is preferred. Patients and
644 physicians should note that combination chemotherapy has shown a survival
645 benefit compared to 5-FU/LV alone. A survival benefit over 5-FU/LV has not been
646 demonstrated with XELODA monotherapy.
- 647 • breast cancer that has spread to other parts of the body and has not responded to
648 treatment with certain other medicines. These medicines include paclitaxel (Taxol®)
649 and anthracycline-containing therapy such as Adriamycin® and doxorubicin.

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

653 **Who should not take XELODA?**

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

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

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

- 659 • **take a blood thinner such as warfarin (Coumadin®). This is very**
660 **important because XELODA may increase the effect of the blood**
661 **thinner. If you are taking blood thinners and XELODA , your doctor**
662 **needs to check how fast your blood clots more frequently and adjust the**
663 **dose of the blood thinner; if needed.**

XELODA® (capecitabine)

- 664 • take phenytoin (Dilantin®). Your doctor needs to test the levels of
665 phenytoin in your blood more often or change your dose of phenytoin.
- 666 • are pregnant. XELODA may not be right for you.
- 667 • have kidney problems. Your doctor may prescribe a different medicine or
668 reduce the XELODA dose.
- 669 • have liver problems. You may need to be checked for liver problems while
670 you take XELODA.
- 671 • take the vitamin folic acid. It may affect how XELODA works.

672 How should I take XELODA?

673 Your doctor will prescribe a dose and treatment plan that is right for *you*. Your doctor may
674 want you to take a combination of 150 mg and 500 mg tablets for each dose. If a
675 combination of tablets is prescribed, you must correctly identify the tablets. Taking the
676 wrong tablets could cause an overdose (too much medicine) or underdose (too little
677 medicine). The 150 mg tablets are light peach in color and have 150 engraved on one side.
678 The 500 mg tablets are peach in color and have 500 engraved on one side. Your doctor
679 may change the amount of medicine you take during your treatment. Your doctor may
680 prescribe XELODA Tablets in combination with Taxotere® or docetaxel injection.

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

XELODA® (capecitabine)

694 What should I avoid while taking XELODA?

- 695 • Women should not become pregnant while taking XELODA. XELODA may harm
696 your unborn child. Use effective birth control while taking XELODA. Tell your doctor
697 if you become pregnant.
- 698 • Men should practice birth control measures while taking XELODA.
- 699 • Do not breast-feed. XELODA may pass through your milk and harm the baby.

700 What are the most common side effects of XELODA?

701 The most common side effects of XELODA are:

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

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

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

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

718 Contact your doctor right away if you have:

- 719 • **Diarrhea:** if you have more than 4 bowel movements each day or any diarrhea at night
- 720 • **Vomiting:** if you vomit more than once in a 24-hour time period
- 721 • **Nausea:** if you lose your appetite, and the amount of food you eat each day is much
722 less than usual

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- 723 • ***Stomatitis:*** if you have pain, redness, swelling or sores in your mouth
- 724 • ***Hand-and-Foot Syndrome:*** if you have pain and swelling or redness of your hands or
725 feet that prevents normal activity
- 726 • ***Fever or Infection:*** if you have a temperature of 100.5°F or greater, or other signs of
727 infection

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

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

- 733 • **Never share XELODA with anyone.**
- 734 • **XELODA should be stored at normal room temperature (about 65° to 85°F).**
- 735 • **Keep this and all other medications out of the reach of children.**
- 736 • **In case of accidental ingestion or if you suspect that more than the prescribed dose**
737 **of this medication has been taken, contact your doctor or local poison control**
738 **center or emergency room IMMEDIATELY.**

739 **General advice about prescription medicines:**

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

743
744 This leaflet summarizes the most important information about XELODA. If you would like more
745 information, talk with your doctor. You can ask your pharmacist or doctor for information about
746 XELODA that is written for health professionals.

- 747
- 748
- 749 **Adriamycin is a registered trademark of Pharmacia & Upjohn Company.**
- 750 **Coumadin is a registered trademark of DuPont Pharma.**
- 751 **Dilantin is a registered trademark of Parke-Davis.**
- 752 **Taxol is a registered trademark of Bristol-Myers Squibb Company.**
- 753 **Taxotere is a registered trademark of Aventis Pharmaceuticals Products Inc.**

754

755 **R_x only**

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Pharmaceuticals

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