

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XELODA® safely and effectively. See full prescribing information for XELODA®.

XELODA® (capecitabine) Tablets, Film Coated for Oral use
Initial U.S. Approval: 1998

WARNING: XELODA-WARFARIN INTERACTION

See full prescribing information for complete boxed warning.

Patients receiving concomitant XELODA and oral coumarin-derivative anticoagulants such as warfarin and phenprocoumon should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. Altered coagulation parameters and/or bleeding, including death, have been reported during concomitant use.

- **Occurrence:** Within several days and up to several months after initiating XELODA therapy; may also be seen within 1 month after stopping XELODA
- **Predisposing factors:** age>60 and diagnosis of cancer

INDICATIONS AND USAGE

XELODA (capecitabine) is a nucleoside metabolic inhibitor with antineoplastic activity indicated for:

- **Adjuvant Colon Cancer** (1.1)
 - Patients with Dukes' C colon cancer
- **Metastatic Colorectal Cancer** (1.1)
 - First-line as monotherapy when treatment with fluoropyrimidine therapy alone is preferred
- **Metastatic Breast Cancer** (1.2)
 - In combination with docetaxel after failure of prior anthracycline-containing therapy
 - As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen

DOSAGE AND ADMINISTRATION

- Take XELODA with water within 30 min after a meal (2)
- Monotherapy: 1250 mg/m² twice daily orally for 2 weeks followed by a one week rest period in 3-week cycles (2.1)
- Adjuvant treatment is recommended for a total of 6 months (8 cycles) (2.1)
- In combination with docetaxel, the recommended dose of XELODA is 1250 mg/m² twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m² as a 1-hour IV infusion every 3 weeks (2.1)
- XELODA dosage may need to be individualized to optimize patient management (2.2)
- Reduce the dose of XELODA by 25% in patients with moderate renal impairment (2.3)

DOSAGE FORMS AND STRENGTHS

- Tablets: 150 mg and 500 mg (3)

CONTRAINDICATIONS

- Dihydropyrimidine dehydrogenase (DPD) deficiency (4.1)
- Severe Renal Impairment (4.2)
- Hypersensitivity (4.3)

WARNINGS AND PRECAUTIONS

- **Diarrhea:** May be severe. Interrupt XELODA treatment immediately until diarrhea resolves or decreases to grade 1. Recommend standard antidiarrheal treatments. (5.1)
- **Coagulopathy:** May result in bleeding, death. Monitor anticoagulant response (e.g., INR) and adjust anticoagulant dose accordingly. (5.2)
- **Cardiotoxicity:** Common in patients with a prior history of coronary artery disease. (5.3)
- **Pregnancy:** Can cause fetal harm. Advise women of the potential risk to the fetus. (5.6, 8.1)
- **Hand-and-Foot Syndrome (Grade 2 or 3):** Interrupt XELODA treatment until the event resolves or decreases in intensity. (5.7)
- **Hyperbilirubinemia (Grade 2 to 4):** Interrupt XELODA treatment immediately until the hyperbilirubinemia resolves or decreases in intensity. (5.8)
- **Hematologic:** Do not treat patients with neutrophil counts <1.5 x 10⁹/L or thrombocyte counts <100 x 10⁹/L. If grade 3-4 neutropenia or thrombocytopenia occurs, stop therapy until condition resolves. (5.9)

ADVERSE REACTIONS

Most common adverse reactions (≥30%) were diarrhea, hand-and-foot syndrome, nausea, vomiting, abdominal pain, fatigue/weakness, and hyperbilirubinemia. Other adverse reactions, including serious adverse reactions, have been reported. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Anticoagulants: Monitor anticoagulant response (INR or prothrombin time) frequently in order to adjust the anticoagulant dose as needed. (5.2, 7.1)
- Phenytoin: Monitor phenytoin levels in patients taking XELODA concomitantly with phenytoin. The phenytoin dose may need to be reduced. (7.1)
- Leucovorin: The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin. (7.1)
- CYP2C9 substrates: Care should be exercised when XELODA is coadministered with CYP2C9 substrates. (7.1)
- Food reduced both the rate and extent of absorption of capecitabine. (2, 7.1, 12.3)

USE IN SPECIFIC POPULATIONS

- **Nursing Mothers:** Discontinue nursing when receiving XELODA treatment. (8.3)
- **Geriatric:** Greater incidence of adverse reactions. Monitoring required. (8.5)
- **Hepatic Impairment:** Monitoring is recommended in patients with mild to moderate hepatic impairment. (8.6)
- **Renal Impairment:** Reduce XELODA starting dose in patients with moderate renal impairment (2.3, 8.7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2013

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FULL PRESCRIBING INFORMATION

WARNING: XELODA-WARFARIN INTERACTION

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 *Warnings and Precautions (5.2) and Drug Interactions (7.1)*]. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinically significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time XELODA was introduced. These events occurred within several days and up to several months after initiating XELODA therapy and, in a few cases, within 1 month after stopping XELODA. These events occurred in patients with and without liver metastases. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy.

1 INDICATIONS AND USAGE

1.1 Colorectal Cancer

- XELODA is indicated as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred. XELODA was non-inferior to 5-fluorouracil and leucovorin (5-FU/LV) for disease-free survival (DFS). Physicians should consider results of combination chemotherapy trials, which have shown improvement in DFS and OS, when prescribing single-agent XELODA in the adjuvant treatment of Dukes' C colon cancer.
- XELODA is indicated as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival benefit over 5-FU/LV has not been demonstrated with XELODA monotherapy. Use of XELODA instead of 5-FU/LV in combinations has not been adequately studied to assure safety or preservation of the survival advantage.

1.2 Breast Cancer

- XELODA in combination with docetaxel is indicated for the treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.
- XELODA monotherapy is also indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated (e.g., patients who have received cumulative doses of 400 mg/m² of doxorubicin or doxorubicin equivalents). Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen.

2 DOSAGE AND ADMINISTRATION

XELODA tablets should be swallowed whole with water within 30 minutes after a meal. XELODA dose is calculated according to body surface area.

44 **2.1 Standard Starting Dose**

45 Monotherapy (Metastatic Colorectal Cancer, Adjuvant Colorectal Cancer, Metastatic Breast Cancer)

46 The recommended dose of XELODA is 1250 mg/m² administered orally twice daily (morning and
47 evening; equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by a 1-week rest period
48 given as 3-week cycles (see **Table 1**).

49 Adjuvant treatment in patients with Dukes' C colon cancer is recommended for a total of 6 months
50 [ie, XELODA 1250 mg/m² orally twice daily for 2 weeks followed by a 1-week rest period, given as
51 3-week cycles for a total of 8 cycles (24 weeks)].

52 **Table 1 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

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

54 In Combination With Docetaxel (Metastatic Breast Cancer)

55 In combination with docetaxel, the recommended dose of XELODA is 1250 mg/m² twice daily for 2
56 weeks followed by a 1-week rest period, combined with docetaxel at 75 mg/m² as a 1-hour
57 intravenous infusion every 3 weeks. Pre-medication, according to the docetaxel labeling, should be
58 started prior to docetaxel administration for patients receiving the XELODA plus docetaxel
59 combination. **Table 1** displays the total daily dose of XELODA by body surface area and the
60 number of tablets to be taken at each dose.

61 **2.2 Dose Management Guidelines**

62 General

63 XELODA dosage may need to be individualized to optimize patient management. Patients should
64 be carefully monitored for toxicity and doses of XELODA should be modified as necessary to
65 accommodate individual patient tolerance to treatment [see *Clinical Studies (14)*]. Toxicity due to
66 XELODA administration may be managed by symptomatic treatment, dose interruptions and
67 adjustment of XELODA dose. Once the dose has been reduced, it should not be increased at a later
68 time. Doses of XELODA omitted for toxicity are not replaced or restored; instead the patient should
69 resume the planned treatment cycles.

70 The dose of phenytoin and the dose of coumarin-derivative anticoagulants may need to be reduced
71 when either drug is administered concomitantly with XELODA [see *Drug Interactions (7.1)*].

72 Monotherapy (Metastatic Colorectal Cancer, Adjuvant Colorectal Cancer, Metastatic Breast Cancer)

73 XELODA dose modification scheme as described below (see **Table 2**) is recommended for the
74 management of adverse reactions.

75 **Table 2 Recommended Dose Modifications of XELODA**

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

76 *National Cancer Institute of Canada Common Toxicity Criteria were used except for the hand-and-foot syndrome [see
77 *Warnings and Precautions (5)*].

78 **In Combination With Docetaxel (Metastatic Breast Cancer)**

79 Dose modifications of XELODA for toxicity should be made according to **Table 2** above for
80 XELODA. At the beginning of a treatment cycle, if a treatment delay is indicated for either
81 XELODA or docetaxel, then administration of both agents should be delayed until the requirements
82 for restarting both drugs are met.

83 The dose reduction schedule for docetaxel when used in combination with XELODA for the
84 treatment of metastatic breast cancer is shown in **Table 3**.

85 **Table 3 Docetaxel Dose Reduction Schedule in Combination with XELODA**

Toxicity NCIC Grades*	Grade 2	Grade 3	Grade 4
1st appearance	Delay treatment until resolved to grade 0-1; Resume treatment with original dose of 75 mg/m ² docetaxel	Delay treatment until resolved to grade 0-1; Resume treatment at 55 mg/m ² of docetaxel.	Discontinue treatment with docetaxel
2nd appearance	Delay treatment until resolved to grade 0-1; Resume treatment at 55 mg/m ² of docetaxel.	Discontinue treatment with docetaxel	-
3rd appearance	Discontinue treatment with docetaxel	-	-

86 *National Cancer Institute of Canada Common Toxicity Criteria were used except for hand-and-foot syndrome [see
87 *Warnings and Precautions (5)*].

88 **2.3 Adjustment of Starting Dose in Special Populations**

89 **Renal Impairment**

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

92 patients with moderate renal impairment (baseline creatinine clearance = 30 to 50 mL/min), a dose
93 reduction to 75% of the XELODA starting dose when used as monotherapy or in combination with
94 docetaxel (from 1250 mg/m² to 950 mg/m² twice daily) is recommended [see Use in Specific
95 Populations (8.7) and Clinical Pharmacology (12.3)]. Subsequent dose adjustment is recommended
96 as outlined in **Table 2** and **Table 3** (depending on the regimen) if a patient develops a grade 2 to 4
97 adverse event [see Warnings and Precautions (5.5)]. The starting dose adjustment recommendations
98 for patients with moderate renal impairment apply to both XELODA monotherapy and XELODA in
99 combination use with docetaxel.

100 Cockcroft and Gault Equation:

101
$$(140 - \text{age [yrs]}) (\text{body wt [kg]})$$

102 Creatinine clearance for males = $\frac{\text{---}}{\text{---}}$

103
$$(72) (\text{serum creatinine [mg/dL]})$$

104 Creatinine clearance for females = 0.85 x male value

105 Geriatrics

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

108 **3 DOSAGE FORMS AND STRENGTHS**

109 XELODA is supplied as biconvex, oblong film-coated tablets for oral administration. Each light
110 peach-colored tablet contains 150 mg of capecitabine and each peach-colored tablet contains 500 mg
111 of capecitabine.

112 **4 CONTRAINDICATIONS**

113 **4.1 Dihydropyrimidine Dehydrogenase (DPD) Deficiency**

114 XELODA is contraindicated in patients with known dihydropyrimidine dehydrogenase (DPD)
115 deficiency.

116 **4.2 Severe Renal Impairment**

117 XELODA is contraindicated in patients with severe renal impairment (creatinine clearance below 30
118 mL/min [Cockcroft and Gault]) [see Use in Specific Populations (8.7) and Clinical
119 Pharmacology (12.3)].

120 **4.3 Hypersensitivity**

121 XELODA is contraindicated in patients with known hypersensitivity to capecitabine or to any of its
122 components. XELODA is contraindicated in patients who have a known hypersensitivity to 5-
123 fluorouracil.

124 **5 WARNINGS AND PRECAUTIONS**

125 General

126 Patients receiving therapy with XELODA should be monitored by a physician experienced in the use
127 of cancer chemotherapeutic agents. Most adverse reactions are reversible and do not need to result in
128 discontinuation, although doses may need to be withheld or reduced [see Dosage and
129 Administration (2.2)].

130 **5.1 Diarrhea**

131 XELODA can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully
132 monitored and given fluid and electrolyte replacement if they become dehydrated. In 875 patients

133 with either metastatic breast or colorectal cancer who received XELODA monotherapy, the median
134 time to first occurrence of grade 2 to 4 diarrhea was 34 days (range from 1 to 369 days). The median
135 duration of grade 3 to 4 diarrhea was 5 days. National Cancer Institute of Canada (NCIC) grade 2
136 diarrhea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an
137 increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an increase
138 of ≥ 10 stools/day or grossly bloody diarrhea or the need for parenteral support. If grade 2, 3 or 4
139 diarrhea occurs, administration of XELODA should be immediately interrupted until the diarrhea
140 resolves or decreases in intensity to grade 1. Following a reoccurrence of grade 2 diarrhea or
141 occurrence of any grade 3 or 4 diarrhea, subsequent doses of XELODA should be decreased [*see*
142 *Dosage and Administration (2.2)*]. Standard antidiarrheal treatments (eg, loperamide) are
143 recommended.

144 Necrotizing enterocolitis (typhlitis) has been reported.

145 **5.2 Coagulopathy**

146 Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy
147 should have their anticoagulant response (INR or prothrombin time) monitored closely with great
148 frequency and the anticoagulant dose should be adjusted accordingly [*see Boxed Warning and Drug*
149 *Interactions (7.1)*].

150 **5.3 Cardiotoxicity**

151 The cardiotoxicity observed with XELODA includes myocardial infarction/ischemia, angina,
152 dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and
153 cardiomyopathy. These adverse reactions may be more common in patients with a prior history of
154 coronary artery disease.

155 **5.4 Dihydropyrimidine Dehydrogenase Deficiency**

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

160 **5.5 Renal Insufficiency**

161 Patients with moderate renal impairment at baseline require dose reduction [*see Dosage and*
162 *Administration (2.3)*]. Patients with mild and moderate renal impairment at baseline should be
163 carefully monitored for adverse reactions. Prompt interruption of therapy with subsequent dose
164 adjustments is recommended if a patient develops a grade 2 to 4 adverse event as outlined in **Table 2**
165 [*see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical*
166 *Pharmacology (12.3)*].

167 **5.6 Pregnancy**

168 XELODA may cause fetal harm when given to a pregnant woman. Capecitabine caused
169 embryolethality and teratogenicity in mice and embryolethality in monkeys when administered
170 during organogenesis. If this drug is used during pregnancy, or if a patient becomes pregnant while
171 receiving XELODA, the patient should be apprised of the potential hazard to the fetus [*see Use in*
172 *Specific Populations (8.1)*].

173 **5.7 Hand-and-Foot Syndrome**

174 Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral
175 erythema) is a cutaneous toxicity. Median time to onset was 79 days (range from 11 to 360 days)
176 with a severity range of grades 1 to 3 for patients receiving XELODA monotherapy in the metastatic
177 setting. Grade 1 is characterized by any of the following: numbness, dysesthesia/paresthesia,
178 tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not

179 disrupt normal activities. Grade 2 hand-and-foot syndrome is defined as painful erythema and
180 swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living.
181 Grade 3 hand-and-foot syndrome is defined as moist desquamation, ulceration, blistering or severe
182 pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or
183 perform activities of daily living. If grade 2 or 3 hand-and-foot syndrome occurs, administration of
184 XELODA should be interrupted until the event resolves or decreases in intensity to grade 1.
185 Following grade 3 hand-and-foot syndrome, subsequent doses of XELODA should be decreased
186 [see *Dosage and Administration (2.2)*].

187 **5.8 Hyperbilirubinemia**

188 In 875 patients with either metastatic breast or colorectal cancer who received at least one dose of
189 XELODA 1250 mg/m² twice daily as monotherapy for 2 weeks followed by a 1-week rest period,
190 grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) of patients and grade 4 (>3 x
191 ULN) hyperbilirubinemia occurred in 3.9% (n=34) of patients. Of 566 patients who had hepatic
192 metastases at baseline and 309 patients without hepatic metastases at baseline, grade 3 or 4
193 hyperbilirubinemia occurred in 22.8% and 12.3%, respectively. Of the 167 patients with grade 3 or 4
194 hyperbilirubinemia, 18.6% (n=31) also had postbaseline elevations (grades 1 to 4, without elevations
195 at baseline) in alkaline phosphatase and 27.5% (n=46) had postbaseline elevations in transaminases
196 at any time (not necessarily concurrent). The majority of these patients, 64.5% (n=20) and 71.7%
197 (n=33), had liver metastases at baseline. In addition, 57.5% (n=96) and 35.3% (n=59) of the 167
198 patients had elevations (grades 1 to 4) at both prebaseline and postbaseline in alkaline phosphatase
199 or transaminases, respectively. Only 7.8% (n=13) and 3.0% (n=5) had grade 3 or 4 elevations in
200 alkaline phosphatase or transaminases.

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

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

211 If drug-related grade 3 to 4 elevations in bilirubin occur, administration of XELODA should be
212 immediately interrupted until the hyperbilirubinemia decreases to ≤3.0 X ULN [see recommended
213 dose modifications under *Dosage and Administration (2.2)*].

214 **5.9 Hematologic**

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

221 Patients with baseline neutrophil counts of <1.5 x 10⁹/L and/or thrombocyte counts of <100 x 10⁹/L
222 should not be treated with XELODA. If unscheduled laboratory assessments during a treatment
223 cycle show grade 3 or 4 hematologic toxicity, treatment with XELODA should be interrupted.

224 **5.10 Geriatric Patients**

225 Patients ≥ 80 years old may experience a greater incidence of grade 3 or 4 adverse reactions. In 875
226 patients with either metastatic breast or colorectal cancer who received XELODA monotherapy,
227 62% of the 21 patients ≥ 80 years of age treated with XELODA experienced a treatment-related
228 grade 3 or 4 adverse event: diarrhea in 6 (28.6%), nausea in 3 (14.3%), hand-and-foot syndrome in 3
229 (14.3%), and vomiting in 2 (9.5%) patients. Among the 10 patients 70 years of age and greater (no
230 patients were >80 years of age) treated with XELODA in combination with docetaxel, 30% (3 out of
231 10) of patients experienced grade 3 or 4 diarrhea and stomatitis, and 40% (4 out of 10) experienced
232 grade 3 hand-and-foot syndrome.

233 Among the 67 patients ≥ 60 years of age receiving XELODA in combination with docetaxel, the
234 incidence of grade 3 or 4 treatment-related adverse reactions, treatment-related serious adverse
235 reactions, withdrawals due to adverse reactions, treatment discontinuations due to adverse reactions
236 and treatment discontinuations within the first two treatment cycles was higher than in the <60 years
237 of age patient group.

238 In 995 patients receiving XELODA as adjuvant therapy for Dukes' C colon cancer after resection of
239 the primary tumor, 41% of the 398 patients ≥ 65 years of age treated with XELODA experienced a
240 treatment-related grade 3 or 4 adverse event: hand-and-foot syndrome in 75 (18.8%), diarrhea in
241 52 (13.1%), stomatitis in 12 (3.0%), neutropenia/granulocytopenia in 11 (2.8%), vomiting in 6
242 (1.5%), and nausea in 5 (1.3%) patients. In patients ≥ 65 years of age (all randomized population;
243 capecitabine 188 patients, 5-FU/LV 208 patients) treated for Dukes' C colon cancer after resection
244 of the primary tumor, the hazard ratios for disease-free survival and overall survival for XELODA
245 compared to 5-FU/LV were 1.01 (95% C.I. 0.80 – 1.27) and 1.04 (95% C.I. 0.79 – 1.37),
246 respectively.

247 **5.11 Hepatic Insufficiency**

248 Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully
249 monitored when XELODA is administered. The effect of severe hepatic dysfunction on the
250 disposition of XELODA is not known [see *Use in Specific Populations (8.6) and Clinical*
251 *Pharmacology (12.3)*].

252 **5.12 Combination With Other Drugs**

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

254 **6 ADVERSE REACTIONS**

255 Because clinical trials are conducted under widely varying conditions, adverse reaction rates
256 observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of
257 another drug and may not reflect the rates observed in practice.

258 **6.1 Adjuvant Colon Cancer**

259 **Table 4** shows the adverse reactions occurring in $\geq 5\%$ of patients from one phase 3 trial in patients
260 with Dukes' C colon cancer who received at least one dose of study medication and had at least one
261 safety assessment. A total of 995 patients were treated with 1250 mg/m² twice a day of XELODA
262 administered for 2 weeks followed by a 1-week rest period, and 974 patients were administered 5-
263 FU and leucovorin (20 mg/m² leucovorin IV followed by 425 mg/m² IV bolus 5-FU on days 1-5
264 every 28 days). The median duration of treatment was 164 days for capecitabine-treated patients and
265 145 days for 5-FU/LV-treated patients. A total of 112 (11%) and 73 (7%) capecitabine and
266 5-FU/LV-treated patients, respectively, discontinued treatment because of adverse reactions. A total
267 of 18 deaths due to all causes occurred either on study or within 28 days of receiving study drug: 8
268 (0.8%) patients randomized to XELODA and 10 (1.0%) randomized to 5-FU/LV.

269 **Table 5** shows grade 3/4 laboratory abnormalities occurring in $\geq 1\%$ of patients from one phase 3
 270 trial in patients with Dukes' C colon cancer who received at least one dose of study medication and
 271 had at least one safety assessment.

272 **Table 4** **Percent Incidence of Adverse Reactions Reported**
 273 **in $\geq 5\%$ of Patients Treated With XELODA or 5-FU/LV for**
 274 **Colon Cancer in the Adjuvant Setting (Safety Population)**

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

	Adjuvant Treatment for Colon Cancer (N=1969)			
	XELODA (N=995)		5-FU/LV (N=974)	
Body System/ Adverse Event	All Grades	Grade 3/4	All Grades	Grade 3/4
<i>Blood and Lymphatic System Disorders</i> Neutropenia	2	<1	8	5
<i>Respiratory Thoracic and Mediastinal Disorders</i> Epistaxis	2	-	5	-

275

276 **Table 5** Percent Incidence of Grade 3/4 Laboratory
277 **Abnormalities Reported in $\geq 1\%$ of Patients Receiving**
278 **XELODA Monotherapy for Adjuvant Treatment of**
279 **Colon Cancer (Safety Population)**

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

280

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

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

287 **6.2 Metastatic Colorectal Cancer**

288 Monotherapy

289 **Table 6** shows the adverse reactions occurring in $\geq 5\%$ of patients from pooling the two phase 3
290 trials in first line metastatic colorectal cancer. A total of 596 patients with metastatic colorectal
291 cancer were treated with 1250 mg/m² twice a day of XELODA administered for 2 weeks followed
292 by a 1-week rest period, and 593 patients were administered 5-FU and leucovorin in the Mayo
293 regimen (20 mg/m² leucovorin IV followed by 425 mg/m² IV bolus 5-FU, on days 1-5, every 28
294 days). In the pooled colorectal database the median duration of treatment was 139 days for
295 capecitabine-treated patients and 140 days for 5-FU/LV-treated patients. A total of 78 (13%) and 63
296 (11%) capecitabine and 5-FU/LV-treated patients, respectively, discontinued treatment because of
297 adverse reactions/intercurrent illness. A total of 82 deaths due to all causes occurred either on study

298 or within 28 days of receiving study drug: 50 (8.4%) patients randomized to XELODA and 32
 299 (5.4%) randomized to 5-FU/LV.

300 **Table 6 Pooled Phase 3 Colorectal Trials: Percent Incidence**
 301 **of Adverse Reactions in ≥5% of Patients**

Adverse Event	XELODA (n=596)			5-FU/LV (n=593)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Number of Patients With > One Adverse Event	96	52	9	94	45	9
Body System/Adverse Event						
GI						
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
Skin and Subcutaneous						
Hand-and-Foot Syndrome	54	17	NA	6	1	NA
Dermatitis	27	1	–	26	1	–
Skin Discoloration	7	<1	–	5	–	–
Alopecia	6	–	–	21	<1	–
General						
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
Neurological						
Peripheral Sensory Neuropathy	10	–	–	4	–	–
Headache	10	1	–	7	–	–
Dizziness*	8	<1	–	8	<1	–
Insomnia	7	–	–	7	–	–
Taste Disturbance	6	1	–	11	<1	1
Metabolism						
Appetite Decreased	26	3	<1	31	2	<1
Dehydration	7	2	<1	8	3	1
Eye						
Eye Irritation	13	–	–	10	<1	–
Vision Abnormal	5	–	–	2	–	–

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

302 – Not observed
303 * Excluding vertigo
304 NA = Not Applicable

305 6.3 Breast Cancer

306 In Combination with Docetaxel

307 The following data are shown for the combination study with XELODA and docetaxel in patients
308 with metastatic breast cancer in **Table 7** and **Table 8**. In the XELODA and docetaxel combination
309 arm the treatment was XELODA administered orally 1250 mg/m² twice daily as intermittent therapy
310 (2 weeks of treatment followed by 1 week without treatment) for at least 6 weeks and docetaxel
311 administered as a 1-hour intravenous infusion at a dose of 75 mg/m² on the first day of each 3-week
312 cycle for at least 6 weeks. In the monotherapy arm docetaxel was administered as a 1-hour
313 intravenous infusion at a dose of 100 mg/m² on the first day of each 3-week cycle for at least 6
314 weeks. The mean duration of treatment was 129 days in the combination arm and 98 days in the
315 monotherapy arm. A total of 66 patients (26%) in the combination arm and 49 (19%) in the
316 monotherapy arm withdrew from the study because of adverse reactions. The percentage of patients
317 requiring dose reductions due to adverse reactions was 65% in the combination arm and 36% in the
318 monotherapy arm. The percentage of patients requiring treatment interruptions due to adverse
319 reactions in the combination arm was 79%. Treatment interruptions were part of the dose
320 modification scheme for the combination therapy arm but not for the docetaxel monotherapy-treated
321 patients.

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Table 7 Percent Incidence of Adverse Events Considered Related or Unrelated to Treatment in $\geq 5\%$ of Patients 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 %
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	–	–
<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	–
Paresthesia	12	<1	–	16	1	–
Dizziness	12	–	–	8	<1	–
Insomnia	8	–	–	10	<1	–
Peripheral Neuropathy	6	–	–	10	1	–
Hypoesthesia	4	<1	–	8	<1	–

Adverse Event	XELODA 1250 mg/m ² /bid With Docetaxel 75 mg/m ² /3 weeks (n=251)			Docetaxel 100 mg/m ² /3 weeks (n=255)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Metabolism						
Anorexia	13	1	–	11	<1	–
Appetite Decreased	10	–	–	5	–	–
Weight Decreased	7	–	–	5	–	–
Dehydration	10	2	–	7	<1	<1
Eye						
Lacrimation Increased	12	–	–	7	<1	–
Conjunctivitis	5	–	–	4	–	–
Eye Irritation	5	–	–	1	–	–
Musculoskeletal						
Arthralgia	15	2	–	24	3	–
Myalgia	15	2	–	25	2	–
Back Pain	12	<1	–	11	3	–
Bone Pain	8	<1	–	10	2	–
Cardiac						
Edema	33	<2	–	34	<3	1
Blood						
Neutropenic Fever	16	3	13	21	5	16
Respiratory						
Dyspnea	14	2	<1	16	2	–
Cough	13	1	–	22	<1	–
Sore Throat	12	2	–	11	<1	–
Epistaxis	7	<1	–	6	–	–
Rhinorrhea	5	–	–	3	–	–
Pleural Effusion	2	1	–	7	4	–
Infection						
Oral Candidiasis	7	<1	–	8	<1	–
Urinary Tract Infection	6	<1	–	4	–	–
Upper Respiratory Tract	4	–	–	5	1	–
Vascular						
Flushing	5	–	–	5	–	–
Lymphoedema	3	<1	–	5	1	–
Psychiatric						
Depression	5	–	–	5	1	–

326
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– Not observed
NA = Not Applicable

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Table 8 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)

Body System/Adverse Event	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

331 Monotherapy

332 The following data are shown for the study in stage IV breast cancer patients who received a dose of
333 1250 mg/m² administered twice daily for 2 weeks followed by a 1-week rest period. The mean
334 duration of treatment was 114 days. A total of 13 out of 162 patients (8%) discontinued treatment
335 because of adverse reactions/intercurrent illness.

336 **Table 9 Percent Incidence of Adverse Reactions Considered Remotely,**
337 **Possibly or Probably Related to Treatment in ≥5% of**
338 **Patients Participating in the Single Arm Trial in Stage IV**
339 **Breast Cancer**

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
	Body System/Adverse Event	Total %	Grade 3 %
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	–	–
General			
Fatigue	41	8	–
Pyrexia	12	1	–
Pain in Limb	6	1	–
Neurological			
Paresthesia	21	1	–
Headache	9	1	–
Dizziness	8	–	–
Insomnia	8	–	–
Metabolism			
Anorexia	23	3	–
Dehydration	7	4	1

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)		
	Body System/Adverse Event	Total %	Grade 3 %
<i>Eye</i> Eye Irritation	15	–	–
<i>Musculoskeletal</i> Myalgia	9	–	–
<i>Cardiac</i> Edema	9	1	–
<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

340 – Not observed
341 NA = Not Applicable

342 6.4 Clinically Relevant Adverse Events in <5% of Patients

343 Clinically relevant adverse events reported in <5% of patients treated with XELODA either as
344 monotherapy or in combination with docetaxol that were considered at least remotely related to
345 treatment are shown below; occurrences of each grade 3 and 4 adverse event are provided in
346 parentheses.

347 Monotherapy (Metastatic Colorectal Cancer, Adjuvant Colorectal Cancer, Metastatic Breast Cancer)

348 *Gastrointestinal:* abdominal distension, dysphagia, proctalgia, ascites (0.1%), gastric ulcer
349 (0.1%), ileus (0.3%), toxic dilation of intestine, gastroenteritis (0.1%)
350 *Skin & Subcutan.:* nail disorder (0.1%), sweating increased (0.1%), photosensitivity reaction
351 (0.1%), skin ulceration, pruritus, radiation recall syndrome (0.2%)
352 *General:* chest pain (0.2%), influenza-like illness, hot flushes, pain (0.1%), hoarseness,
353 irritability, difficulty in walking, thirst, chest mass, collapse, fibrosis (0.1%),
354 hemorrhage, edema, sedation
355 *Neurological:* insomnia, ataxia (0.5%), tremor, dysphasia, encephalopathy (0.1%), abnormal
356 coordination, dysarthria, loss of consciousness (0.2%), impaired balance
357 *Metabolism:* increased weight, cachexia (0.4%), hypertriglyceridemia (0.1%),
358 hypokalemia, hypomagnesemia
359 *Eye:* conjunctivitis
360 *Respiratory:* cough (0.1%), epistaxis (0.1%), asthma (0.2%), hemoptysis, respiratory
361 distress (0.1%), dyspnea
362 *Cardiac:* tachycardia (0.1%), bradycardia, atrial fibrillation, ventricular extrasystoles,
363 extrasystoles, myocarditis (0.1%), pericardial effusion
364 *Infections:* laryngitis (1.0%), bronchitis (0.2%), pneumonia (0.2%), bronchopneumonia
365 (0.2%), keratoconjunctivitis, sepsis (0.3%), fungal infections (including
366 candidiasis) (0.2%)
367 *Musculoskeletal:* myalgia, bone pain (0.1%), arthritis (0.1%), muscle weakness
368 *Blood & Lymphatic:* leukopenia (0.2%), coagulation disorder (0.1%), bone marrow depression
369 (0.1%), idiopathic thrombocytopenia purpura (1.0%), pancytopenia (0.1%)

370 *Vascular:* hypotension (0.2%), hypertension (0.1%), lymphoedema (0.1%), pulmonary
371 embolism (0.2%), cerebrovascular accident (0.1%)
372 *Psychiatric:* depression, confusion (0.1%)
373 *Renal:* renal impairment (0.6%)
374 *Ear:* vertigo
375 *Hepatobiliary:* hepatic fibrosis (0.1%), hepatitis (0.1%), cholestatic hepatitis (0.1%),
376 abnormal liver function tests
377 *Immune System:* drug hypersensitivity (0.1%)
378 *Postmarketing:* hepatic failure, lacrimal duct stenosis

379 XELODA In Combination With Docetaxel (Metastatic Breast Cancer)

380 *Gastrointestinal:* ileus (0.4%), necrotizing enterocolitis (0.4%), esophageal ulcer (0.4%),
381 hemorrhagic diarrhea (0.8%)
382 *Neurological:* ataxia (0.4%), syncope (1.2%), taste loss (0.8%), polyneuropathy (0.4%),
383 migraine (0.4%)
384 *Cardiac:* supraventricular tachycardia (0.4%)
385 *Infection:* neutropenic sepsis (2.4%), sepsis (0.4%), bronchopneumonia (0.4%)
386 *Blood & Lymphatic:* agranulocytosis (0.4%), prothrombin decreased (0.4%)
387 *Vascular:* hypotension (1.2%), venous phlebitis and thrombophlebitis (0.4%), postural
388 hypotension (0.8%)
389 *Renal:* renal failure (0.4%)
390 *Hepatobiliary:* jaundice (0.4%), abnormal liver function tests (0.4%), hepatic failure (0.4%),
391 hepatic coma (0.4%), hepatotoxicity (0.4%)
392 *Immune System:* hypersensitivity (1.2%)

393 **7 DRUG INTERACTIONS**

394 **7.1 Drug-Drug Interactions**

395 Anticoagulants

396 Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA
397 concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon
398 [see *Boxed Warning*]. These events occurred within several days and up to several months after
399 initiating XELODA therapy and, in a few cases, within 1 month after stopping XELODA. These
400 events occurred in patients with and without liver metastases. In a drug interaction study with single-
401 dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin [see
402 *Clinical Pharmacology (12.3)*]. The maximum observed INR value increased by 91%. This
403 interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its
404 metabolites.

405 Phenytoin

406 The level of phenytoin should be carefully monitored in patients taking XELODA and phenytoin
407 dose may need to be reduced [see *Dosage and Administration (2.2)*]. Postmarketing reports indicate
408 that some patients receiving XELODA and phenytoin had toxicity associated with elevated
409 phenytoin levels. Formal drug-drug interaction studies with phenytoin have not been conducted, but
410 the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine
411 and/or its metabolites.

412 Leucovorin

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

416 CYP2C9 substrates

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

420 **7.2 Drug-Food Interaction**

421 Food was shown to reduce both the rate and extent of absorption of capecitabine [*see Clinical*
422 *Pharmacology (12.3)*]. In all clinical trials, patients were instructed to administer XELODA within
423 30 minutes after a meal. It is recommended that XELODA be administered with food [*see Dosage*
424 *and Administration (2)*].

425 **8 USE IN SPECIFIC POPULATIONS**

426 **8.1 Pregnancy: Category D**

427 XELODA can cause fetal harm when administered to a pregnant woman. Capecitabine at doses of
428 198 mg/kg/day during organogenesis caused malformations and embryo death in mice. In separate
429 pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.2 times the
430 corresponding values in patients administered the recommended daily dose. Malformations in mice
431 included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky
432 tail and dilation of cerebral ventricles. At doses of 90 mg/kg/day, capecitabine given to pregnant
433 monkeys during organogenesis caused fetal death. This dose produced 5'-DFUR AUC values about
434 0.6 times the corresponding values in patients administered the recommended daily dose.

435 There are no adequate and well controlled studies of XELODA in pregnant women. If this drug is
436 used during pregnancy, or if a patient becomes pregnant while receiving XELODA, the patient
437 should be apprised of the potential hazard to the fetus. Women should be advised to avoid becoming
438 pregnant while receiving treatment with XELODA [*see Warnings and Precautions (5.6)*].

439 **8.3 Nursing Mothers**

440 Lactating mice given a single oral dose of capecitabine excreted significant amounts of capecitabine
441 metabolites into the milk. It is not known whether this drug is excreted in human milk. Because
442 many drugs are excreted in human milk and because of the potential for serious adverse reactions in
443 nursing infants from capecitabine, a decision should be made whether to discontinue nursing or to
444 discontinue the drug, taking into account the importance of the drug to the mother.

445 **8.4 Pediatric Use**

446 The safety and effectiveness of XELODA in pediatric patients have not been established. No clinical
447 benefit was demonstrated in two single arm trials in pediatric patients with newly diagnosed
448 brainstem gliomas and high grade gliomas. In both trials, pediatric patients received an
449 investigational pediatric formulation of capecitabine concomitantly with and following completion
450 of radiation therapy (total dose of 5580 cGy in 180 cGy fractions). The relative bioavailability of the
451 investigational formulation to XELODA was similar.

452
453 The first trial was conducted in 22 pediatric patients (median age 8 years, range 5-17 years) with
454 newly diagnosed non-disseminated intrinsic diffuse brainstem gliomas and high grade gliomas. In
455 the dose-finding portion of the trial, patients received capecitabine with concomitant radiation
456 therapy at doses ranging from 500 mg/m² to 850 mg/m² every 12 hours for up to 9 weeks. After a
457 2 week break, patients received 1250 mg/m² capecitabine every 12 hours on Days 1-14 of a 21-day
458 cycle for up to 3 cycles. The maximum tolerated dose (MTD) of capecitabine administered
459 concomitantly with radiation therapy was 650 mg/m² every 12 hours. The major dose limiting
460 toxicities were palmar-plantar erythrodysesthesia and alanine aminotransferase (ALT) elevation.

461

462 The second trial was conducted in 34 additional pediatric patients with newly diagnosed non-
463 disseminated intrinsic diffuse brainstem gliomas (median age 7 years, range 3-16 years) and 10
464 pediatric patients who received the MTD of capecitabine in the dose-finding trial and met the
465 eligibility criteria for this trial. All patients received 650 mg/m² capecitabine every 12 hours with
466 concomitant radiation therapy for up to 9 weeks. After a 2 week break, patients received 1250
467 mg/m² capecitabine every 12 hours on Days 1-14 of a 21-day cycle for up to 3 cycles.

468
469 There was no improvement in one-year progression-free survival rate and one-year overall survival
470 rate in pediatric patients with newly diagnosed intrinsic brainstem gliomas who received
471 capecitabine relative to a similar population of pediatric patients who participated in other clinical
472 trials.

473
474 The adverse reaction profile of capecitabine was consistent with the known adverse reaction profile
475 in adults, with the exception of laboratory abnormalities which occurred more commonly in pediatric
476 patients. The most frequently reported laboratory abnormalities (per-patient incidence \geq 40%) were
477 increased ALT (75%), lymphocytopenia (73%), leukopenia (73%), hypokalemia (68%),
478 thrombocytopenia (57%), hypoalbuminemia (55%), neutropenia (50%), low hematocrit (50%),
479 hypocalcemia (48%), hypophosphatemia (45%) and hyponatremia (45%).

481 **8.5 Geriatric Use**

482 Physicians should pay particular attention to monitoring the adverse effects of XELODA in the
483 elderly [*see Warnings and Precautions (5.11)*].

484 **8.6 Hepatic Insufficiency**

485 Exercise caution when patients with mild to moderate hepatic dysfunction due to liver metastases are
486 treated with XELODA. The effect of severe hepatic dysfunction on XELODA is not known [*see*
487 *Warnings and Precautions (5.12) and Clinical Pharmacology (12.3)*].

488 **8.7 Renal Insufficiency**

489 Patients with moderate (creatinine clearance = 30 to 50 mL/min) and severe (creatinine clearance
490 <30 mL/min) renal impairment showed higher exposure for capecitabine, 5-FDUR, and FBAL than
491 in those with normal renal function [*see Contraindications (4.2), Warnings and Precautions (5.5),*
492 *Dosage and Administration (2.3), and Clinical Pharmacology (12.3)*].

493 **10 OVERDOSAGE**

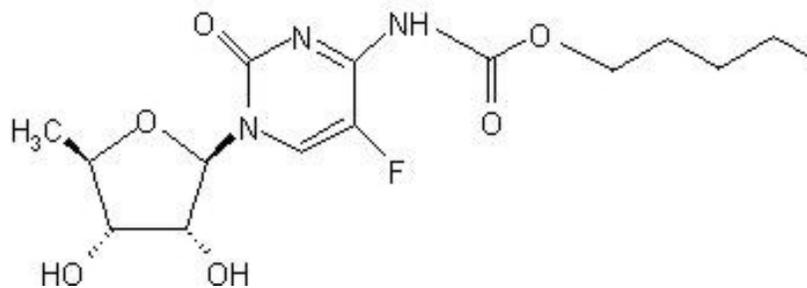
494 The manifestations of acute overdose would include nausea, vomiting, diarrhea, gastrointestinal
495 irritation and bleeding, and bone marrow depression. Medical management of overdose should
496 include customary supportive medical interventions aimed at correcting the presenting clinical
497 manifestations.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

500 Single doses of XELODA were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg (2.4,
501 4.8, and 9.6 times the recommended human daily dose on a mg/m² basis).

502 **11 DESCRIPTION**

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

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



508

509 Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at
510 20°C.

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

517 12 CLINICAL PHARMACOLOGY

518 12.1 Mechanism of Action

519 Enzymes convert capecitabine to 5-fluorouracil (5-FU) *in vivo*. Both normal and tumor cells
520 metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine
521 triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First,
522 FdUMP and the folate cofactor, N⁵⁻¹⁰-methylenetetrahydrofolate, bind to thymidylate synthase (TS)
523 to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from
524 2'-deoxyuridylate. Thymidylate is the necessary precursor of thymidine triphosphate, which is
525 essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division.
526 Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine
527 triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA
528 processing and protein synthesis.

529 12.3 Pharmacokinetics

530 Absorption

531 Following oral administration of 1255 mg/m² BID to cancer patients, capecitabine reached peak
532 blood levels in about 1.5 hours (T_{max}) with peak 5-FU levels occurring slightly later, at 2 hours.
533 Food reduced both the rate and extent of absorption of capecitabine with mean C_{max} and AUC_{0-∞}
534 decreased by 60% and 35%, respectively. The C_{max} and AUC_{0-∞} of 5-FU were also reduced by food
535 by 43% and 21%, respectively. Food delayed T_{max} of both parent and 5-FU by 1.5 hours [see
536 *Warnings and Precautions* (5), *Dosage and Administration* (2), and *Drug-Food Interaction* (7.2)].

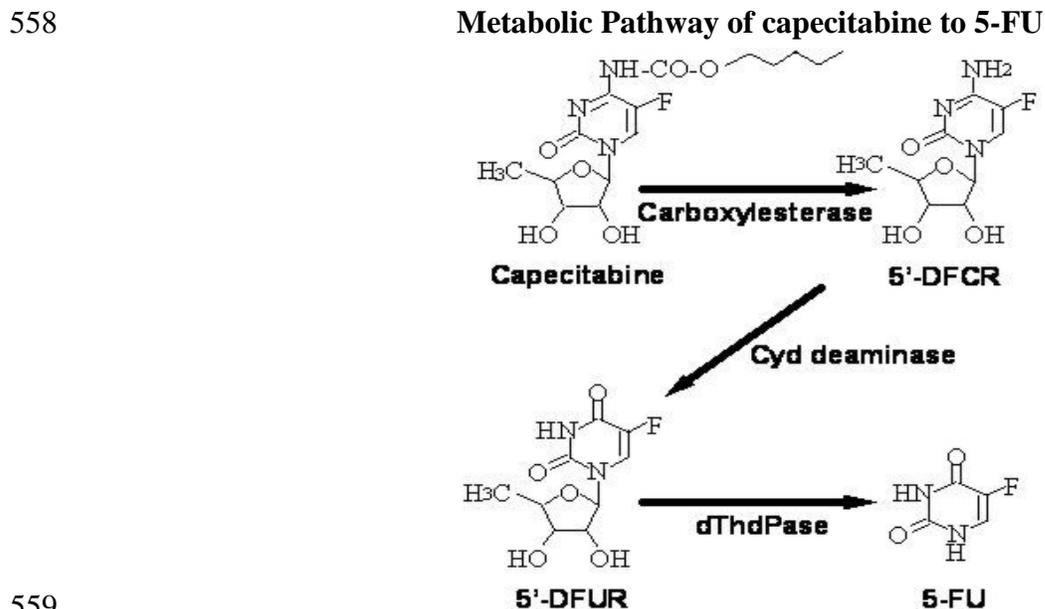
537 The pharmacokinetics of XELODA and its metabolites have been evaluated in about 200 cancer
538 patients over a dosage range of 500 to 3500 mg/m²/day. Over this range, the pharmacokinetics of
539 XELODA and its metabolite, 5'-DFCR were dose proportional and did not change over time. The
540 increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the
541 increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The interpatient
542 variability in the C_{max} and AUC of 5-FU was greater than 85%.

543 Distribution

544 Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-
545 dependent. Capecitabine was primarily bound to human albumin (approximately 35%). XELODA
546 has a low potential for pharmacokinetic interactions related to plasma protein binding.

547 **Bioactivation and Metabolism**

548 Capecitabine is extensively metabolized enzymatically to 5-FU. In the liver, a 60 kDa
549 carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR).
550 Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-
551 DFCR to 5'-DFUR. The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR
552 to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase. Some
553 human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.
554 Following oral administration of XELODA 7 days before surgery in patients with colorectal cancer,
555 the median ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 2.9 (range from
556 0.9 to 8.0). These ratios have not been evaluated in breast cancer patients or compared to 5-FU
557 infusion.



559

560 The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine
561 metabolism, to the much less toxic 5-fluoro-5, 6-dihydro-fluorouracil (FUH₂). Dihydropyrimidinase
562 cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, β-ureido-
563 propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine.

564 In vitro enzymatic studies with human liver microsomes indicated that capecitabine and its
565 metabolites (5'-DFUR, 5'-DFCR, 5-FU, and FBAL) did not inhibit the metabolism of test substrates
566 by cytochrome P450 isoenzymes 1A2, 2A6, 3A4, 2C19, 2D6, and 2E1.

567 **Excretion**

568 Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered
569 capecitabine dose is recovered in urine. Fecal excretion is minimal (2.6%). The major metabolite
570 excreted in urine is FBAL which represents 57% of the administered dose. About 3% of the
571 administered dose is excreted in urine as unchanged drug. The elimination half-life of both parent
572 capecitabine and 5-FU was about 0.75 hour.

573 **Effect of Age, Gender, and Race on the Pharmacokinetics of Capecitabine**

574 A population analysis of pooled data from the two large controlled studies in patients with metastatic
575 colorectal cancer (n=505) who were administered XELODA at 1250 mg/m² twice a day indicated
576 that gender (202 females and 303 males) and race (455 white/Caucasian patients, 22 black patients,
577 and 28 patients of other race) have no influence on the pharmacokinetics of 5'-DFUR, 5-FU and

578 FBAL. Age has no significant influence on the pharmacokinetics of 5'-DFUR and 5-FU over the
579 range of 27 to 86 years. A 20% increase in age results in a 15% increase in AUC of FBAL [*see*
580 *Warnings and Precautions (5.11) and Dosage and Administration (2.3)*].

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

586 ***Effect of Hepatic Insufficiency***

587 XELODA has been evaluated in 13 patients with mild to moderate hepatic dysfunction due to liver
588 metastases defined by a composite score including bilirubin, AST/ALT and alkaline phosphatase
589 following a single 1255 mg/m² dose of XELODA. Both AUC_{0-∞} and C_{max} of capecitabine increased
590 by 60% in patients with hepatic dysfunction compared to patients with normal hepatic function
591 (n=14). The AUC_{0-∞} and C_{max} of 5-FU were not affected. In patients with mild to moderate hepatic
592 dysfunction due to liver metastases, caution should be exercised when XELODA is administered.
593 The effect of severe hepatic dysfunction on XELODA is not known [*see Warnings and*
594 *Precautions (5.11) and Use in Special Populations (8.6)*].

595 ***Effect of Renal Insufficiency***

596 Following oral administration of 1250 mg/m² capecitabine twice a day to cancer patients with
597 varying degrees of renal impairment, patients with moderate (creatinine clearance = 30 to 50
598 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment showed 85% and 258%
599 higher systemic exposure to FBAL on day 1 compared to normal renal function patients (creatinine
600 clearance >80 mL/min). Systemic exposure to 5'-DFUR was 42% and 71% greater in moderately
601 and severely renal impaired patients, respectively, than in normal patients. Systemic exposure to
602 capecitabine was about 25% greater in both moderately and severely renal impaired patients [*see*
603 *Dosage and Administration (2.3), Contraindications (4.2), Warnings and Precautions (5.5), and Use*
604 *in Special Populations (8.7)*].

605 ***Effect of Capecitabine on the Pharmacokinetics of Warfarin***

606 In four patients with cancer, chronic administration of capecitabine (1250 mg/m² bid) with a single
607 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and decreased its clearance
608 by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8-fold, and the maximum
609 observed mean INR value was increased by 91% [*see Boxed Warning and Drug Interactions (7.1)*].

610 ***Effect of Antacids on the Pharmacokinetics of Capecitabine***

611 When Maalox® (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing antacid,
612 was administered immediately after XELODA (1250 mg/m², n=12 cancer patients), AUC and C_{max}
613 increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for
614 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of
615 XELODA.

616 ***Effect of Capecitabine on the Pharmacokinetics of Docetaxel and Vice Versa***

617 A Phase 1 study evaluated the effect of XELODA on the pharmacokinetics of docetaxel (Taxotere®)
618 and the effect of docetaxel on the pharmacokinetics of XELODA was conducted in 26 patients with
619 solid tumors. XELODA was found to have no effect on the pharmacokinetics of docetaxel (C_{max} and
620 AUC) and docetaxel has no effect on the pharmacokinetics of capecitabine and the 5-FU precursor
621 5'-DFUR.

622 **13 NONCLINICAL TOXICOLOGY**

623 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

624 Adequate studies investigating the carcinogenic potential of XELODA have not been conducted.
625 Capecitabine was not mutagenic *in vitro* to bacteria (Ames test) or mammalian cells (Chinese
626 hamster V79/HPRT gene mutation assay). Capecitabine was clastogenic *in vitro* to human peripheral
627 blood lymphocytes but not clastogenic *in vivo* to mouse bone marrow (micronucleus test).
628 Fluorouracil causes mutations in bacteria and yeast. Fluorouracil also causes chromosomal
629 abnormalities in the mouse micronucleus test *in vivo*.

630 Impairment of Fertility

631 In studies of fertility and general reproductive performance in female mice, oral capecitabine doses
632 of 760 mg/kg/day (about 2300 mg/m²/day) disturbed estrus and consequently caused a decrease in
633 fertility. In mice that became pregnant, no fetuses survived this dose. The disturbance in estrus was
634 reversible. In males, this dose caused degenerative changes in the testes, including decreases in the
635 number of spermatocytes and spermatids. In separate pharmacokinetic studies, this dose in mice
636 produced 5'-DFUR AUC values about 0.7 times the corresponding values in patients administered
637 the recommended daily dose.

638 **14 CLINICAL STUDIES**

639 **14.1 Adjuvant Colon Cancer**

640 A multicenter randomized, controlled phase 3 clinical trial in patients with Dukes' C colon cancer
641 (X-ACT) provided data concerning the use of XELODA for the adjuvant treatment of patients with
642 colon cancer. The primary objective of the study was to compare disease-free survival (DFS) in
643 patients receiving XELODA to those receiving IV 5-FU/LV alone. In this trial, 1987 patients were
644 randomized either to treatment with XELODA 1250 mg/m² orally twice daily for 2 weeks followed
645 by a 1-week rest period, given as 3-week cycles for a total of 8 cycles (24 weeks) or IV bolus 5-FU
646 425 mg/m² and 20 mg/m² IV leucovorin on days 1 to 5, given as 4-week cycles for a total of 6 cycles
647 (24 weeks). Patients in the study were required to be between 18 and 75 years of age with
648 histologically-confirmed Dukes' stage C colon cancer with at least one positive lymph node and to
649 have undergone (within 8 weeks prior to randomization) complete resection of the primary tumor
650 without macroscopic or microscopic evidence of remaining tumor. Patients were also required to
651 have no prior cytotoxic chemotherapy or immunotherapy (except steroids), and have an ECOG
652 performance status of 0 or 1 (KPS ≥ 70%), ANC ≥ 1.5x10⁹/L, platelets ≥ 100x10⁹/L, serum
653 creatinine ≤ 1.5 ULN, total bilirubin ≤ 1.5 ULN, AST/ALT ≤ 2.5 ULN and CEA within normal
654 limits at time of randomization.

655 The baseline demographics for XELODA and 5-FU/LV patients are shown in **Table 10**. The
656 baseline characteristics were well-balanced between arms.

Table 10 Baseline Demographics

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

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All patients with normal renal function or mild renal impairment began treatment at the full starting dose of 1250 mg/m² orally twice daily. The starting dose was reduced in patients with moderate renal impairment (calculated creatinine clearance 30 to 50 mL/min) at baseline [see *Dosage and Administration (2.3)*]. Subsequently, for all patients, doses were adjusted when needed according to toxicity. Dose management for XELODA included dose reductions, cycle delays and treatment interruptions (see **Table 11**).

665

Table 11 Summary of Dose Modifications in X-ACT Study

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

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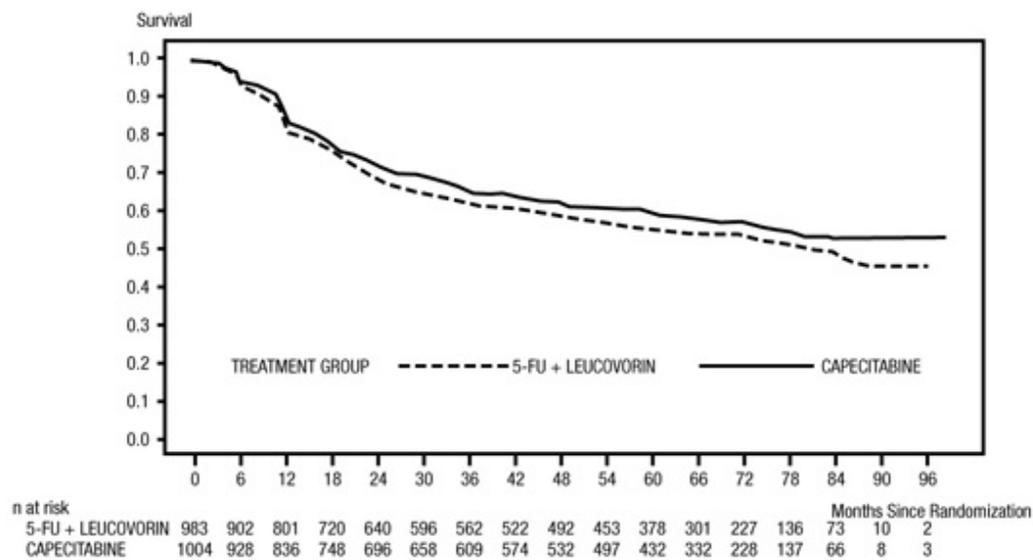
The median follow-up at the time of the analysis was 83 months (6.9 years). The hazard ratio for DFS for XELODA compared to 5-FU/LV was 0.88 (95% C.I. 0.77 – 1.01) (see **Table 12** and **Figure 1**). Because the upper 2-sided 95% confidence limit of hazard ratio was less than 1.20, XELODA was non-inferior to 5-FU/LV. The choice of the non-inferiority margin of 1.20 corresponds to the retention of approximately 75% of the 5-FU/LV effect on DFS. The hazard ratio for XELODA compared to 5-FU/LV with respect to overall survival was 0.86 (95% C.I. 0.74 – 1.01). The 5-year overall survival rates were 71.4% for XELODA and 68.4% for 5-FU/LV (see **Figure 2**).

675 **Table 12** Efficacy of XELODA vs 5-FU/LV in Adjuvant
 676 Treatment of Colon Cancer^a

<i>All Randomized Population</i>	XELODA (n=1004)	5-FU/LV (n=983)
Median follow-up (months)	83	83
5-year Disease-free Survival Rates (%)^b	59.1	54.6
Hazard Ratio (XELODA/5-FU/LV) (95% C.I. for Hazard Ratio) p-value ^c	0.88 (0.77 - 1.01) p = 0.068	

677 ^aApproximately 93.4% had 5-year DFS information
 678 ^bBased on Kaplan-Meier estimates
 679 ^cTest of superiority of XELODA vs 5-FU/LV (Wald chi-square test)
 680

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



683
 684 ^aXELODA has been demonstrated to be non-inferior to 5-FU/LV.

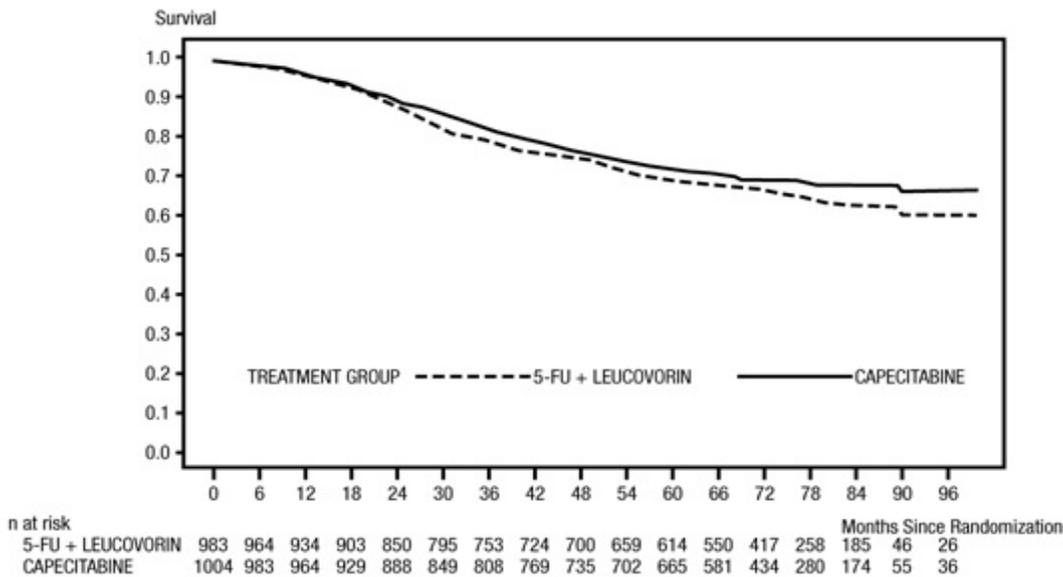
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Figure 2

**Kaplan-Meier Estimates of Overall Survival
(All Randomized Population)**

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688

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14.2 Metastatic Colorectal Cancer

690

General

691

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

701

Monotherapy

702

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

711

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

716

The baseline demographics for XELODA and 5-FU/LV patients are shown in **Table 13**.

717 **Table 13** **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)

718
719 The efficacy endpoints for the two phase 3 trials are shown in **Table 14** and **Table 15**.

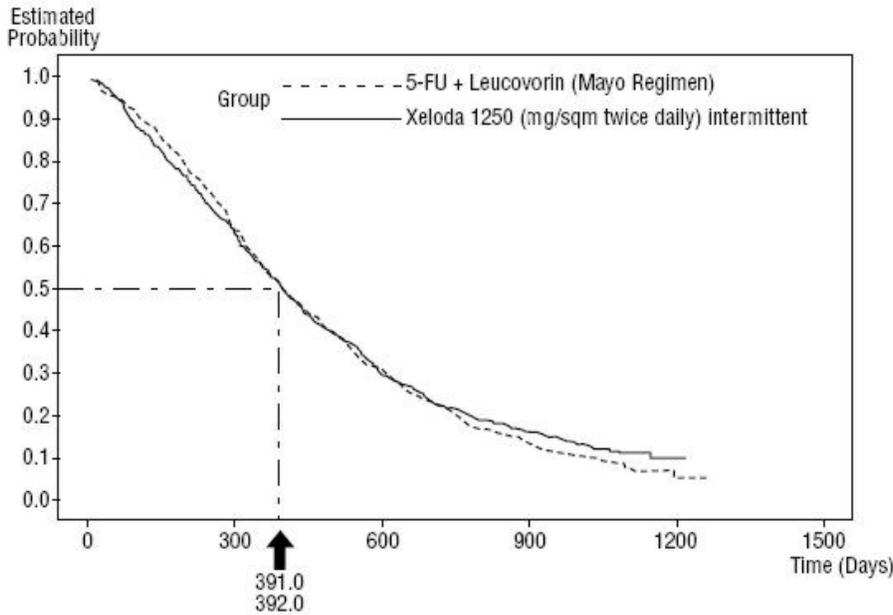
720 **Table 14** **Efficacy of XELODA vs 5-FU/LV in Colorectal Cancer**
721 **(Study 1)**

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

722
723 **Table 15** **Efficacy of XELODA vs 5-FU/LV in Colorectal Cancer**
724 **(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)	

726 **Figure 3** **Kaplan-Meier Curve for Overall Survival of Pooled**
 727 **Data (Studies 1 and 2)**



728
 729 XELODA was superior to 5-FU/LV for objective response rate in Study 1 and Study 2. The
 730 similarity of XELODA and 5-FU/LV in these studies was assessed by examining the potential
 731 difference between the two treatments. In order to assure that XELODA has a clinically meaningful
 732 survival effect, statistical analyses were performed to determine the percent of the survival effect of
 733 5-FU/LV that was retained by XELODA. The estimate of the survival effect of 5-FU/LV was
 734 derived from a meta-analysis of ten randomized studies from the published literature comparing 5-
 735 FU to regimens of 5-FU/LV that were similar to the control arms used in these Studies 1 and 2. The
 736 method for comparing the treatments was to examine the worst case (95% confidence upper bound)
 737 for the difference between 5-FU/LV and XELODA, and to show that loss of more than 50% of the
 738 5-FU/LV survival effect was ruled out. It was demonstrated that the percent of the survival effect of
 739 5-FU/LV maintained was at least 61% for Study 2 and 10% for Study 1. The pooled result is
 740 consistent with a retention of at least 50% of the effect of 5-FU/LV. It should be noted that these
 741 values for preserved effect are based on the upper bound of the 5-FU/LV vs XELODA difference.
 742 These results do not exclude the possibility of true equivalence of XELODA to 5-FU/LV (see
 743 **Table 14, Table 15, and Figure 3**).

744 **14.3 Breast Cancer**

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

747 In Combination With Docetaxel

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

755 XELODA in combination with docetaxel was assessed in an open-label, multicenter, randomized
 756 trial in 75 centers in Europe, North America, South America, Asia, and Australia. A total of 511
 757 patients with metastatic breast cancer resistant to, or recurring during or after an anthracycline-

758 containing therapy, or relapsing during or recurring within 2 years of completing an anthracycline-
 759 containing adjuvant therapy were enrolled. Two hundred and fifty-five (255) patients were
 760 randomized to receive XELODA 1250 mg/m² twice daily for 14 days followed by 1 week without
 761 treatment and docetaxel 75 mg/m² as a 1-hour intravenous infusion administered in 3-week cycles.
 762 In the monotherapy arm, 256 patients received docetaxel 100 mg/m² as a 1-hour intravenous
 763 infusion administered in 3-week cycles. Patient demographics are provided in **Table 16**.

764 **Table 16** **Baseline Demographics and Clinical Characteristics**
 765 **XELODA and Docetaxel Combination vs Docetaxel in**
 766 **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%)

767 ¹Includes 10 patients in combination and 18 patients in monotherapy arms treated with an anthracenedione
 768

769 XELODA in combination with docetaxel resulted in statistically significant improvement in time to
 770 disease progression, overall survival and objective response rate compared to monotherapy with
 771 docetaxel as shown in **Table 17**, **Figure 4**, and **Figure 5**.

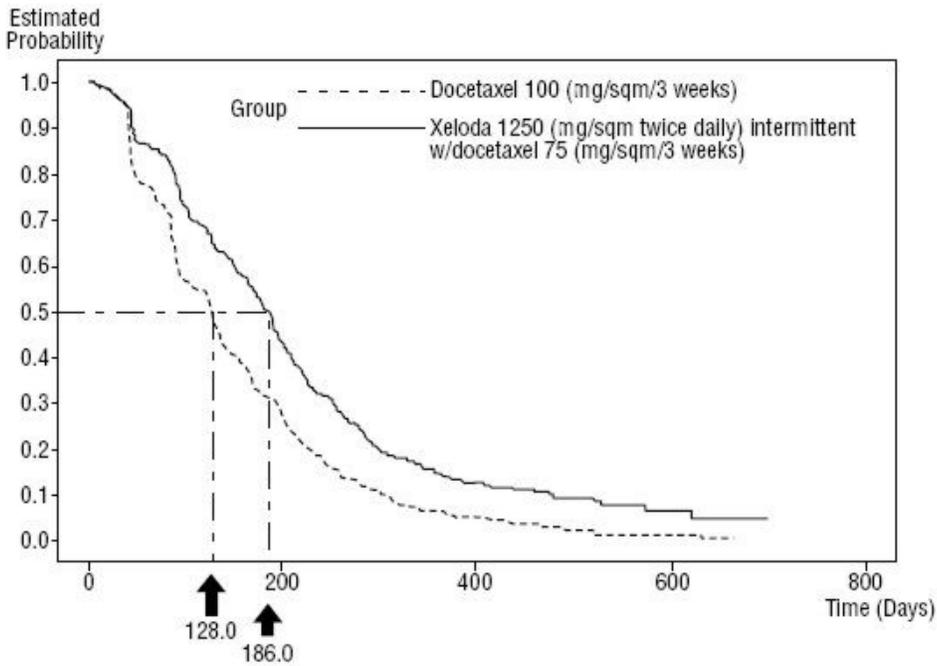
772 **Table 17 Efficacy of XELODA and Docetaxel Combination vs**
 773 **Docetaxel Monotherapy**

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

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

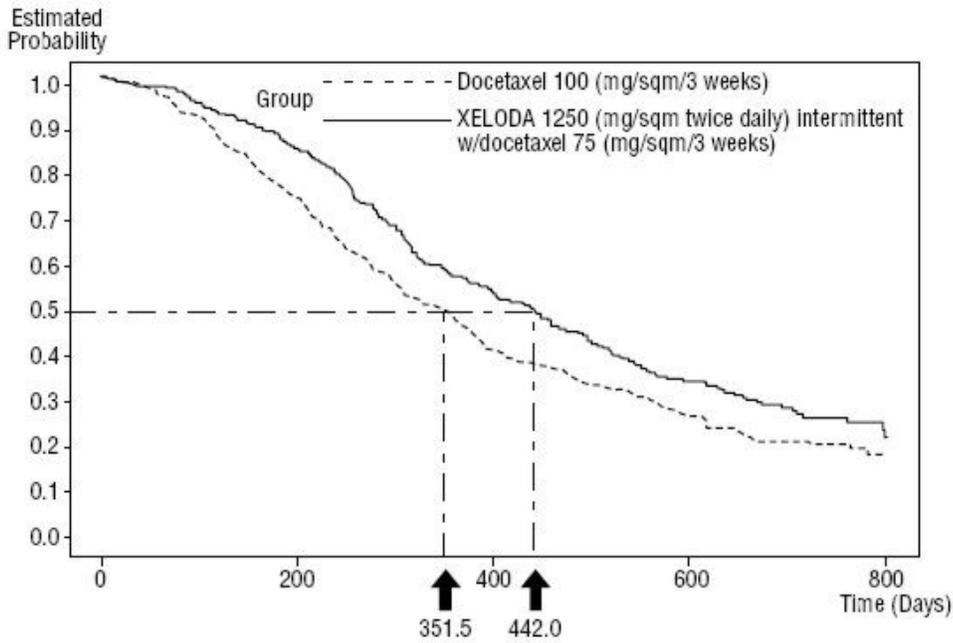
776 ² NA = Not Applicable
 777

778 **Figure 4 Kaplan-Meier Estimates for Time to Disease**
 779 **Progression XELODA and Docetaxel vs Docetaxel**



780

781 **Figure 5** Kaplan-Meier Estimates of Survival XELODA
782 and Docetaxel vs Docetaxel



783

784 Monotherapy

785 The antitumor activity of XELODA as a monotherapy was evaluated in an open-label single-arm
786 trial conducted in 24 centers in the US and Canada. A total of 162 patients with stage IV breast
787 cancer were enrolled. The primary endpoint was tumor response rate in patients with measurable
788 disease, with response defined as a $\geq 50\%$ decrease in sum of the products of the perpendicular
789 diameters of bidimensionally measurable disease for at least 1 month. XELODA was administered at
790 a dose of 1255 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period and given as 3-week
791 cycles. The baseline demographics and clinical characteristics for all patients ($n=162$) and those with
792 measurable disease ($n=135$) are shown in **Table 18**. Resistance was defined as progressive disease
793 while on treatment, with or without an initial response, or relapse within 6 months of completing
794 treatment with an anthracycline-containing adjuvant chemotherapy regimen.

795 **Table 18** **Baseline Demographics and Clinical Characteristics**
 796 **Single-Arm Breast Cancer Trial**

	Patients With Measurable Disease (n=135)	All Patients (n=162)
<i>Age</i> (median, years)	55	56
<i>Karnofsky PS</i>	90	90
<i>No. Disease Sites</i>		
1-2	43 (32%)	60 (37%)
3-4	63 (46%)	69 (43%)
>5	29 (22%)	34 (21%)
<i>Dominant Site of Disease</i>		
Visceral ¹	101 (75%)	110 (68%)
Soft Tissue	30 (22%)	35 (22%)
Bone	4 (3%)	17 (10%)
<i>Prior Chemotherapy</i>		
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%)

797 ¹Lung, pleura, liver, peritoneum

798 ²Includes 2 patients treated with an anthracenedione

799

800 Antitumor responses for patients with disease resistant to both paclitaxel and an anthracycline are
 801 shown in **Table 19**.

802 **Table 19** **Response Rates in Doubly-Resistant Patients Single-Arm**
 803 **Breast Cancer Trial**

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

804 ¹Includes 2 patients treated with an anthracenedione

805 ²From date of first response

806

807 For the subgroup of 43 patients who were doubly resistant, the median time to progression was 102
 808 days and the median survival was 255 days. The objective response rate in this population was
 809 supported by a response rate of 18.5% (1 CR, 24 PRs) in the overall population of 135 patients with
 810 measurable disease, who were less resistant to chemotherapy (see **Table 18**). The median time to
 811 progression was 90 days and the median survival was 306 days.

812 **15 REFERENCES**

- 813 1. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous
814 drugs in healthcare settings. 2004. U.S. Department of Health and Human Services,
815 Public Health Service, Centers for Disease Control and Prevention, National Institute for
816 Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
- 817 2. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling
818 Occupational Exposure to Hazardous Drugs. OSHA, 1999.
819 http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
- 820 3. American Society of Health-System Pharmacists. ASHP Guidelines on Handling
821 Hazardous Drugs: *Am J Health-Syst Pharm.* 2006;63:1172-1193.
- 822 4. Polovich M., White JM, Kelleher LO (eds). Chemotherapy and biotherapy guidelines
823 and recommendations for practice (2nd ed.) 2005. Pittsburgh, PA: Oncology Nursing
824 Society.

825 **16 HOW SUPPLIED/STORAGE AND HANDLING**

826 **150 mg**

- 827 Color: Light peach
828 Engraving: XELODA on one side and 150 on the other
829 150 mg tablets are packaged in bottles of 60 (NDC 0004-1100-20).

830 **500 mg**

- 831 Color: Peach
832 Engraving: XELODA on one side and 500 on the other
833 500 mg tablets are packaged in bottles of 120 (NDC 0004-1101-50).

834 **Storage and Handling**

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

837 Care should be exercised in the handling of XELODA. XELODA tablets should not be cut or
838 crushed. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage
839 of tablets. If powder from broken XELODA tablets contacts the skin, wash the skin immediately
840 and thoroughly with soap and water. If XELODA contacts the mucous membranes, flush thoroughly
841 with water.

842 Procedures for the proper handling and disposal of anticancer drugs should be considered. Several
843 guidelines on the subject have been published.¹⁻⁴

844 **17 PATIENT COUNSELING INFORMATION**

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

846 Patients and patients' caregivers should be informed of the expected adverse effects of XELODA,
847 particularly nausea, vomiting, diarrhea, and hand-and-foot syndrome, and should be made aware that
848 patient-specific dose adaptations during therapy are expected and necessary [*see Dosage and*
849 *Administration (2.2)*]. As described below, patients taking XELODA should be informed of the need
850 to interrupt treatment immediately if moderate or severe toxicity occurs. Patients should be
851 encouraged to recognize the common grade 2 toxicities associated with XELODA treatment.

852 Diarrhea

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

856 Nausea

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

860 Vomiting

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

864 Hand-and-Foot Syndrome

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

868 Stomatitis

869 Patients experiencing grade 2 stomatitis (painful erythema, edema or ulcers of the mouth or tongue,
870 but able to eat) or greater should be instructed to stop taking XELODA immediately. Initiation of
871 symptomatic treatment is recommended [*see Dosage and Administration (2.2)*].

872 Fever and Neutropenia

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

875 **Patient Package Insert**

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

881 **What is XELODA?**

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

885 XELODA is used to treat:

- 886 – cancer of the colon after surgery
- 887 – cancer of the colon or rectum (colorectal cancer) that has spread to other parts of the body
888 (metastatic colorectal cancer). You should know that in studies, other medicines showed
889 improved survival when they were taken together with 5-FU and leucovorin. In studies,
890 XELODA was no worse than 5-FU and leucovorin taken together but did not improve survival
891 compared to these two medicines.
- 892 – breast cancer that has spread to other parts of the body (metastatic breast cancer) together with
893 another medicine called docetaxel (TAXOTERE[®])

- 894 – breast cancer that has spread to other parts of the body and has not improved after treatment with
895 other medicines such as paclitaxel (TAXOL[®]) and anthracycline-containing medicine such as
896 Adriamycin[™] and doxorubicin

897 **What is the most important information about XELODA?**

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

903 **Who should not take XELODA?**

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

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

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

- 911 – take a blood thinner such as warfarin (COUMADIN). This is very important because XELODA
912 may increase the effect of the blood thinner. If you are taking blood thinners and XELODA, your
913 doctor needs to check more often how fast your blood clots and change the dose of the blood
914 thinner, if needed.
915 – take phenytoin (DILANTIN[®]). Your doctor needs to test the levels of phenytoin in your blood
916 more often or change your dose of phenytoin.
917 – are pregnant or think you may be pregnant. XELODA may harm your unborn child.
918 – have kidney problems. Your doctor may prescribe a different medicine or lower the XELODA
919 dose.
920 – have liver problems. You may need to be checked for liver problems while you take XELODA.
921 – have heart problems because you could have more side effects related to your heart.
922 – take the vitamin folic acid. It may affect how XELODA works.

923 **How should I take XELODA?**

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

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

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

- 941 – Women should not become pregnant while taking XELODA. XELODA may harm your unborn
942 child. Use effective birth control while taking XELODA. Tell your doctor if you become
943 pregnant.
944 – Do not breast-feed. XELODA may pass through your milk and harm your baby.
945 – Men should use birth control while taking XELODA

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

947 The most common side effects of XELODA are:

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

955 These side effects may differ when taking XELODA with docetaxel (TAXOTERE). Please consult
956 your doctor for possible side effects that may be caused by taking XELODA with docetaxel
957 (TAXOTERE).

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

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

- 964 – **Diarrhea:** if you have an additional 4 bowel movements each day beyond what is normal or any
965 diarrhea at night
966 – **Vomiting:** if you vomit more than once in a 24-hour time period
967 – **Nausea:** if you lose your appetite, and the amount of food you eat each day is much less than
968 usual
969 – **Stomatitis:** if you have pain, redness, swelling or sores in your mouth
970 – **Hand-and-Foot Syndrome:** if you have pain, swelling or redness of your hands or feet that
971 prevents normal activity
972 – **Fever or Infection:** if you have a temperature of 100.5°F or greater, or other signs of infection

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

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

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

984 **General advice about prescription medicines:**

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

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

991 XELODA is a registered trademark of Hoffmann-La Roche Inc.

992 For full TAXOTERE prescribing information, please refer to TAXOTERE Package Insert.

993

994 XELODA[®] (capecitabine)

Distributed by:

Genentech USA, Inc.

A Member of the Roche Group

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South San Francisco, CA 94080-4990

995

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