XELODA®
(capecitabine)
TABLETS

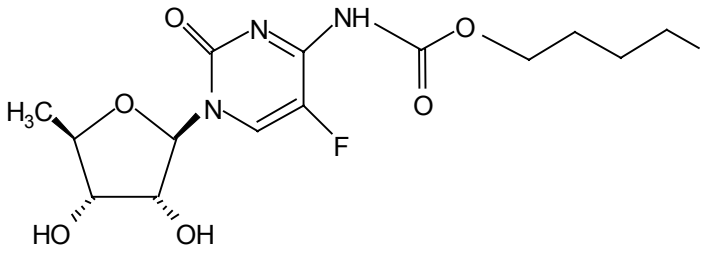
WARNING

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

DESCRIPTION

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

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



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

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

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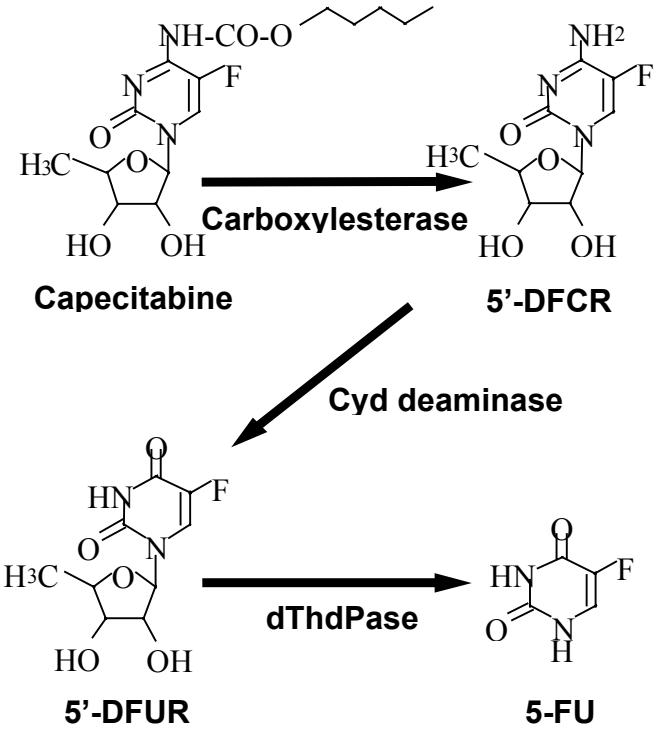
500 mg capecitabine. The inactive ingredients in XELODA include: anhydrous lactose, croscarmellose sodium, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate and purified water. The peach or light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide,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

CLINICAL PHARMACOLOGY

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

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

Metabolic Pathway of capecitabine to 5-FU



Mechanism of Action: Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N^{5-10}-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from 2'-deoxyuridylate.

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Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

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

Human Pharmacokinetics: The pharmacokinetics of XELODA and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m^2/day. Over this range, the pharmacokinetics of XELODA and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The elimination half-life of both parent capecitabine and 5-FU was about ¾ of an hour. The inter-patient variability in the C_{max} and AUC of 5-FU was greater than 85%.

Following oral administration of 825 mg/m^2 capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower C_{max} and 24% lower AUC for capecitabine than the Caucasian patients (n=22). Japanese patients had also about 25% lower C_{max} and 34% lower AUC for FBAL than the Caucasian patients. The clinical significance of these differences is unknown. No significant differences occurred in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU).

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

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

Capecitabine is extensively metabolized enzymatically to 5-FU. The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism, to the much less toxic 5-fluoro-5, 6-dihydro-fluorouracil (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine.

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

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

Special Populations:

A population analysis of pooled data from the two large controlled studies in patients with colorectal cancer (n=505) who were administered XELODA at 1250 mg/m^2 twice a day indicated that gender (202 females and 303 males) and race (455 white/caucasian patients, 22 black patients, and 28 patients of other race) have no influence on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL. Age has no significant influence on the pharmacokinetics of 5'-DFUR and 5-FU over the range of 27 to 86 years. A 20% increase in age results in a 15% increase in AUC of FBAL (see WARNINGS and DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: XELODA has been evaluated in 13 patients with mild to moderate hepatic dysfunction due to liver metastases defined by a composite score including bilirubin, AST/ALT and alkaline phosphatase following a single 1255 mg/m^2 dose of XELODA. Both $AUC_{0-\infty}$ and C_{max} of capecitabine increased by 60% in patients with hepatic dysfunction compared to patients with normal hepatic function (n=14). The $AUC_{0-\infty}$ and C_{max} of 5-FU were not affected. In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when XELODA is administered. The effect of severe hepatic dysfunction on XELODA is not known (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: Following oral administration of 1250 mg/m^2 capecitabine twice a day to cancer patients with varying degrees of renal impairment, patients with moderate (creatinine clearance = 30 to 50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment showed 85% and 258% higher systemic exposure to FBAL on day 1 compared to normal renal function patients (creatinine clearance >80 mL/min). Systemic exposure to 5'-DFUR was 42% and 71% greater in moderately and severely renal impaired patients, respectively, than in normal patients. Systemic exposure to capecitabine was about 25% greater in both moderately and severely renal impaired patients (see CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions:

Anticoagulants: In four patients with cancer, chronic administration of capecitabine (1250 mg/m^2 bid) with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin

by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8-fold, and the maximum observed mean INR value was increased by 91% (see Boxed WARNING and PRECAUTIONS: *Drug-Drug Interactions*).

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

Antacid: When Maalox® (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after XELODA (1250 mg/m^2, n=12 cancer patients), AUC and C_{max} increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of XELODA.

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

CLINICAL STUDIES

Colorectal Carcinoma: 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/m^2/day in two divided doses, n=39), intermittent therapy with capecitabine (2510 mg/m^2/day in two divided doses, n=34), and intermittent therapy with capecitabine in combination with oral leucovorin (LV) (capecitabine 1657 mg/m^2/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/m^2 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.

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/m^2 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/m^2 leucovorin IV followed by 425 mg/m^2 IV bolus 5-FU, on days 1 to 5, every 28 days).

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.

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

Table 1. Baseline Demographics of Controlled Colorectal Trials

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

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

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

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

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

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

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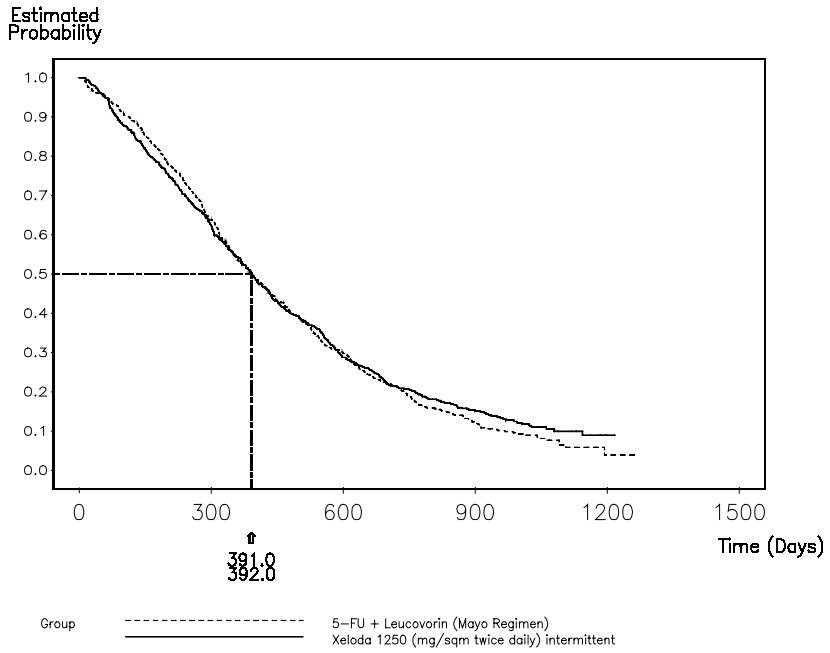
Figure 1. Kaplan-Meier Curve for Overall Survival of Pooled Data (Studies 1 and 2)



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

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

Breast Cancer Combination Therapy: The dose of XELODA used in phase 3 clinical trial in combination with docetaxel was based on the results of a phase 1 study, where a range of doses of docetaxel administered in 3-week cycles in combination with an intermittent regimen of XELODA (14 days of treatment, followed by a 7-day rest period) were evaluated. The

combination dose regimen was selected based on the tolerability profile of the 75 mg/m^2 administered in 3-week cycles of docetaxel in combination with 1250 mg/m^2 twice daily for 14 days of XELODA administered in 3-week cycles. The approved dose of 100 mg/m^2 of docetaxel administered in 3-week cycles was the control arm of the phase 3 study.

XELODA in combination with docetaxel was assessed in an open-label, multicenter, randomized trial in 75 centers in Europe, North America, South America, Asia, and Australia. A total of 511 patients with metastatic breast cancer resistant to, or recurring during or after an anthracycline-containing therapy, or relapsing during or recurring within 2 years of completing an anthracycline-containing adjuvant therapy were enrolled. Two hundred and fifty-five (255) patients were randomized to receive XELODA 1250 mg/m^2 twice daily for 14 days followed by 1 week without treatment and docetaxel 75 mg/m^2 as a 1-hour intravenous infusion administered in 3-week cycles. In the monotherapy arm, 256 patients received docetaxel 100 mg/m^2 as a 1-hour intravenous infusion administered in 3-week cycles. Patient demographics are provided in Table 4.

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Table 4. Baseline Demographics and Clinical Characteristics XELODA and Docetaxel Combination vs Docetaxel in Breast Cancer Trial

	XELODA + Docetaxel (n=255)	Docetaxel (n=256)
Age (median, years)	52	51
Karnofsky PS (median)	90	90
Site of Disease		
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%)
Prior Chemotherapy		
Anthracycline[1]	255 (100%)	256 (100%)
5-FU	196 (77%)	189 (74%)
Paclitaxel	25 (10%)	22 (9%)
Resistance to an Anthracycline		
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%)
No. of Prior Chemotherapy Regimens for Treatment of Metastatic Disease		
0	89 (35%)	80 (31%)
1	123 (48%)	135 (53%)
2	43 (17%)	39 (15%)
3	0 (0%)	2 (1%)

[1]Includes 10 patients in combination and 18 patients in monotherapy arms treated with an anthracenedione

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

Table 5. Efficacy of XELODA and Docetaxel Combination vs Docetaxel Monotherapy

Efficacy Parameter	Combination Therapy	Monotherapy	p-value	Hazard Ratio
Time to Disease Progression				
Median Days	186	128	0.0001	0.643
95% C.I.	(165-198)	(105-136)		
Overall Survival				
Median Days	442	352	0.0126	0.775
95% C.I.	(375-497)	(298-387)		
Response Rate[1]	32%	22%	0.009	NA[2]

[1] The response rate reported represents a reconciliation of the investigator and IRC assessments performed by the sponsor according to a predefined algorithm.
[2] NA = Not Applicable

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

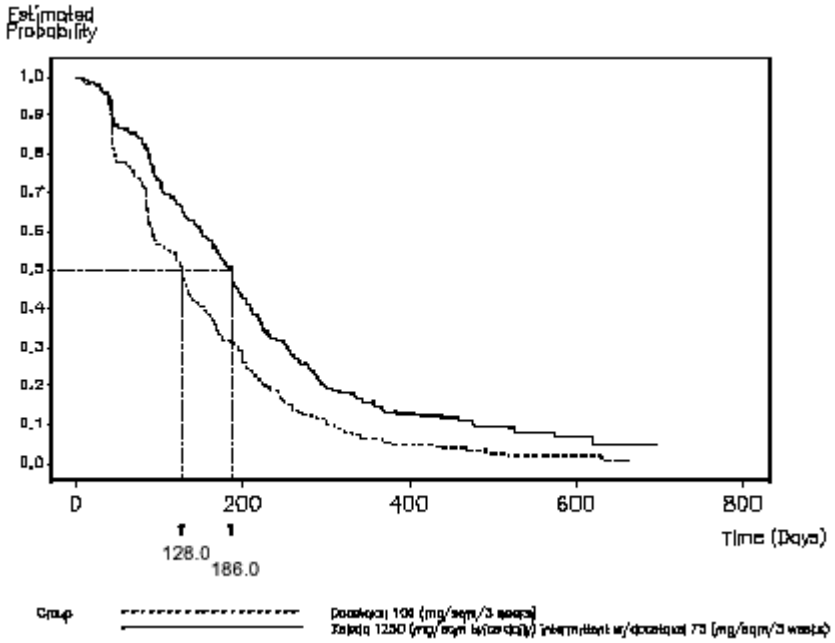
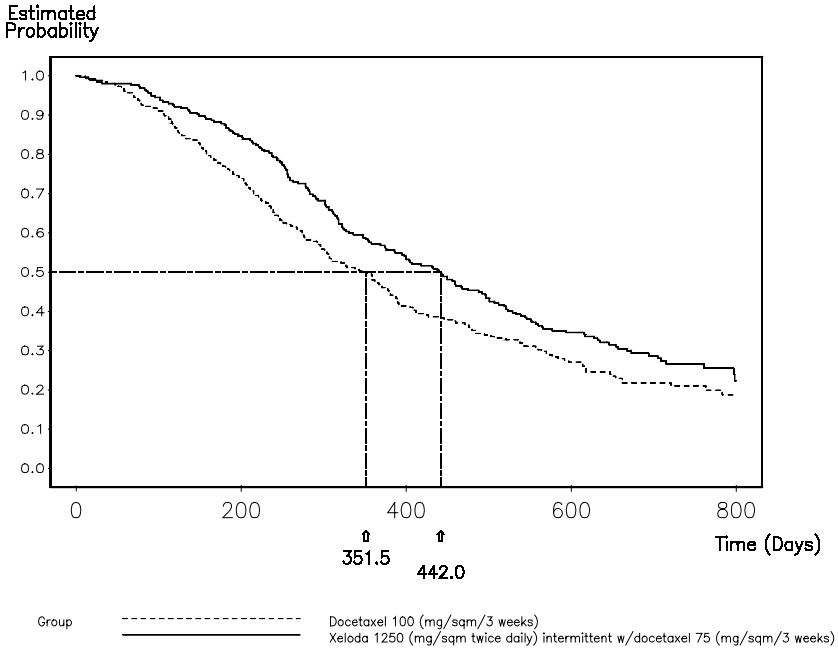


Figure 3. Kaplan-Meier Estimates of Survival XELODA and Docetaxel vs Docetaxel



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Breast Cancer Monotherapy: The antitumor activity of XELODA as a monotherapy was evaluated in an open-label single-arm trial conducted in 24 centers in the US and Canada. A total of 162 patients with stage IV breast cancer were enrolled. The primary endpoint was tumor response rate in patients with measurable disease, with response defined as a ≥50% decrease in sum of the products of the perpendicular diameters of bidimensionally measurable disease for at least 1 month. XELODA was administered at a dose of 1255 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period and given as 3-week cycles. The baseline demographics and clinical characteristics for all patients (n=162) and those with measurable disease (n=135) are shown in Table 6. Resistance was 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 chemotherapy regimen.

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

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

[1]Lung, pleura, liver, peritoneum
[2]Includes 2 patients treated with an anthracenedione

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

Table 7. Response Rates in Doubly-Resistant Patients Single-Arm Breast Cancer Trial

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

[1]Includes 2 patients treated with an anthracenedione
[2]From date of first response

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

INDICATIONS AND USAGE

Colorectal 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.

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

Breast Cancer Monotherapy: 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, eg, patients who have received cumulative doses of 400 mg/m^2 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.

CONTRAINDICATIONS

XELODA is contraindicated in patients with known hypersensitivity to capecitabine or to any of its components. XELODA is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil. XELODA is contraindicated in patients with known dihydropyrimidine dehydrogenase (DPD) deficiency. XELODA is also contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]) (see CLINICAL PHARMACOLOGY: *Special Populations)*.

WARNINGS

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

Coagulopathy: See Boxed WARNING.

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

Necrotizing enterocolitis (typhlitis) has been reported.

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

with XELODA in combination with docetaxel, 30% (3 out of 10) of patients experienced grade 3 or 4 diarrhea and stomatitis, and 40% (4 out of 10) experienced grade 3 hand-and-foot syndrome.

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

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

PRECAUTIONS

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

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

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

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Following grade 3 hand-and-foot syndrome, subsequent doses of XELODA should be decreased (see DOSAGE AND ADMINISTRATION).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Drug-Drug Interactions:

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

Anticoagulants: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly (see Boxed WARNING and CLINICAL PHARMACOLOGY). Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. 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. In a drug interaction study with single dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites (see CLINICAL PHARMACOLOGY).

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

	XELODA (n=596)			5-FU/LV (n=593)		
	Total %	**Grade 3 %**	**Grade 4 %**	**Total %**	**Grade 3 %**	**Grade 4 %**
Number of Patients With > One Adverse Event	96	52	9	94	45	9
Body System/Adverse Event						
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

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

– Not observed
* Excluding vertigo
NA = Not Applicable

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

mg/m^2 on the first day of each 3-week cycle for at least 6 weeks. In the monotherapy arm docetaxel was administered as a 1-hour intravenous infusion at a dose of 100 mg/m^2 on the first day of each 3-week cycle for at least 6 weeks. The mean duration of treatment was 129 days in the combination arm and 98 days in the monotherapy arm. A total of 66 patients (26%) in the combination arm and 49 (19%) in the monotherapy arm withdrew from the study because of adverse events. The percentage of patients requiring dose reductions due to adverse events were 65% in the combination arm and 36% in the monotherapy arm. The percentage of patients requiring treatment interruptions due to adverse events in the combination arm was 79%. Treatment interruptions were part of the dose modification scheme for the combination therapy arm but not for the docetaxel monotherapy-treated patients.

Table 9. Percent Incidence of Adverse Events Considered Related or Unrelated to Treatment in ≥5% of Patients Participating in the XELODA and Docetaxel Combination vs Docetaxel Monotherapy Study

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

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Adverse Event	XELODA 1250 mg/m²/bidWith Docetaxel 75 mg/m²/3 weeks (n=251)			Docetaxel 100 mg/m²/3 weeks (n=255)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
General						
Pyrexia	28	2	–	34	2	–
Asthenia	26	4	<1	25	6	–
Fatigue	22	4	–	27	6	–
Weakness	16	2	–	11	2	–
Pain in Limb	13	<1	–	13	2	–
Lethargy	7	–	–	6	2	–
Pain	7	<1	–	5	1	–
Chest Pain (non-cardiac)	4	<1	–	6	2	–
Influenza-like Illness	5	–	–	5	–	–
Neurological						
Taste Disturbance	16	<1	–	14	<1	–
Headache	15	3	–	15	2	–
Paresthesia	12	<1	–	16	1	–
Dizziness	12	–	–	8	<1	–
Insomnia	8	–	–	10	<1	–
Peripheral Neuropathy	6	–	–	10	1	–
Hypoaesthesia	4	<1	–	8	<1	–
Metabolism						
Anorexia	13	1	–	11	<1	–
Appetite Decreased	10	–	–	5	–	–
Weight Decreased	7	–	–	5	–	–
Dehydration	10	2	–	7	<1	<1
Eye						
Lacrimation Increased	12	–	–	7	<1	–
Conjunctivitis	5	–	–	4	–	–
Eye Irritation	5	–	–	1	–	–
Musculoskeletal						
Arthralgia	15	2	–	24	3	–
Myalgia	15	2	–	25	2	–
Back Pain	12	<1	–	11	3	–
Bone Pain	8	<1	–	10	2	–
Cardiac						
Edema	33	<2	–	34	<3	1

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Adverse Event	XELODA 1250 mg/m²/bidWith Docetaxel 75 mg/m²/3 weeks (n=251)			Docetaxel 100 mg/m²/3 weeks (n=255)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Blood						
Neutropenic Fever	16	3	13	21	5	16
Respiratory						
Dyspnea	14	2	<1	16	2	–
Cough	13	1	–	22	<1	–
Sore Throat	12	2	–	11	<1	–
Epistaxis	7	<1	–	6	–	–
Rhinorrhea	5	–	–	3	–	–
Pleural Effusion	2	1	–	7	4	–
Infection						
Oral Candidiasis	7	<1	–	8	<1	–
Urinary Tract Infection	6	<1	–	4	–	–
Upper Respiratory Tract	4	–	–	5	1	–
Vascular						
Flushing	5	–	–	5	–	–
Lymphoedema	3	<1	–	5	1	–
Psychiatric						
Depression	5	–	–	5	1	–

– Not observed
NA = Not Applicable

Table 10. Percent of Patients With Laboratory Abnormalities Participating in the XELODA and Docetaxel Combination vs Docetaxel Monotherapy Study

Adverse Event	XELODA 1250 mg/m²/bid With Docetaxel 75 mg/m²/ 3 weeks (n=251)			Docetaxel 100 mg/m²/ 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

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

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

Adverse Event	**Phase 2 Trial in Stage IV Breast Cancer (n=162)**		
Body System/Adverse Event	**Total**	**Grade 3**	**Grade 4**
GI			
Diarrhea	57	12	3
Nausea	53	4	–
Vomiting	37	4	–
Stomatitis	24	7	–
Abdominal Pain	20	4	–
Constipation	15	1	–
Dyspepsia	8	–	–
Skin and Subcutaneous			
Hand-and-Foot Syndrome	57	11	NA
Dermatitis	37	1	–
Nail Disorder	7	–	–
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
Eye			
Eye Irritation	15	–	–
Musculoskeletal			
Myalgia	9	–	–
Cardiac			
Edema	9	1	–

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

– Not observed
NA = Not Applicable

OTHER ADVERSE EVENTS:

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

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

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

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

Cardiac: supraventricular tachycardia (0.39)

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

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

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

Renal: renal failure (0.39)

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

Immune System: hypersensitivity (1.20)

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

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

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

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

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

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

Eye: conjunctivitis

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

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

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

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

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

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

Psychiatric: depression, confusion (0.1)

Renal: renal impairment (0.6)

Ear: vertigo

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

Immune System: drug hypersensitivity (0.1)

Postmarketing: hepatic failure

OVERDOSAGE

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

Single doses of XELODA were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg (2.4, 4.8, and 9.6 times the recommended human daily dose on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

The recommended dose of XELODA is 1250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles. XELODA tablets should be swallowed with water within 30 minutes after a meal. In combination with docetaxel, the recommended dose of XELODA is 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period, combined with docetaxel at 75mg/m^2 as a 1-hour intravenous infusion every 3 weeks. Pre-medication, according to the docetaxel labeling, should be started prior to docetaxel administration for patients receiving the XELODA plus docetaxel combination. Table 12 displays the total daily dose by body surface area and the number of tablets to be taken at each dose.

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Table 12. XELODA Dose Calculation According to Body Surface Area

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

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

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

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

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

Table 13. XELODA in Combination With Docetaxel Dose Reduction Schedule

Toxicity NCIC Grades*	Grade 2	Grade 3	Grade 4
1st appearance	Grade 2 occurring during the 14 days of XELODA treatment: interrupt XELODA treatment until resolved to grade 0-1. Treatment may be resumed during the cycle at the same dose of XELODA. Doses of XELODA missed during a treatment cycle are not to be replaced. Prophylaxis for toxicities should be implemented where possible.	Grade 3 occurring during the 14 days of XELODA treatment: interrupt the XELODA treatment until resolved to grade 0-1. Treatment may be resumed during the cycle at 75% of the XELODA dose. Doses of XELODA missed during a treatment cycle are not to be replaced. Prophylaxis for toxicities should be implemented where possible.	Discontinue treatment unless treating physician considers it to be in the best interest of the patient to continue with XELODA at 50% of original dose.

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

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

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

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

Table 14. Recommended Dose Modifications

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	Interrupt until resolved to grade 0-1	75%
-3rd appearance	Interrupt until resolved to grade 0-1	50%
-4th appearance	Discontinue treatment permanently	
• *Grade 3*		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance	Interrupt until resolved to grade 0-1	50%
-3rd appearance	Discontinue treatment permanently	
• *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%

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

Dosage modifications are not recommended for grade 1 events. Therapy with XELODA should be interrupted upon the occurrence of a grade 2 or 3 adverse experience. Once the adverse event has resolved or decreased in intensity to grade 1, then XELODA therapy may be restarted at full dose or as adjusted according to Table 14. If a grade 4 experience occurs, therapy should be discontinued or interrupted until resolved or decreased to grade 1, and therapy should be restarted at 50% of the original dose. Doses of XELODA omitted for toxicity are not replaced or restored; instead the patient should resume the planned treatment cycles.

Adjustment of Starting Dose in Special Populations:

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

Renal Impairment: No adjustment to the starting dose of XELODA is recommended in patients with mild renal impairment (creatinine clearance = 51 to80 mL/min [Cockroft and Gault, as

shown below]). In patients with moderate renal impairment (baseline creatinine clearance = 30 to50 mL/min), a dose reduction to 75% of the XELODA starting dose when used as monotherapy or in combination with docetaxel (from 1250 mg/m^2 to 950 mg/m^2 twice daily) is recommended (see CLINICAL PHARMACOLOGY: *Special Populations*). Subsequent dose adjustment is recommended as outlined in Table 14 if a patient develops a grade 2 to 4 adverse event (see WARNINGS).

Cockroft and Gault Equation:

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

Creatinine clearance for females = 0.85 x male value

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

HOW SUPPLIED

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

150 mg

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

500 mg

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

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

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

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PATIENT PACKAGE INSERT (text only):

Patient Information

XELODA® (capecitabine) Tablets

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

What is XELODA?

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

- cancer of the colon or rectum that has spread to other parts of the body (metastatic colorectal cancer) when fluoropyrimidine therapy alone is preferred. Patients and physicians should note that 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.

- breast cancer that has spread to other parts of the body and has not responded to treatment with certain other medicines. These medicines include paclitaxel (Taxol®) and anthracycline-containing therapy such as Adriamycin® and doxorubicin.

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

Who should not take XELODA?

1. DO NOT TAKE XELODA IF YOU

- are nursing a baby. Tell your doctor if you are nursing. XELODA may pass to the baby in your milk and harm the baby.

- are allergic to 5-fluorouracil.

- are allergic to capecitabine or to any of its ingredients.

- have a known lack of the enzyme DPD (dihydropyrimidine dehydrogenase).

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2. TELL YOUR DOCTOR IF YOU

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

- take phenytoin (Dilantin®). Your doctor needs to test the levels of phenytoin in your blood more often or change your dose of phenytoin.

- are pregnant. XELODA may not be right for you.

- have kidney problems. Your doctor may prescribe a different medicine or reduce the XELODA dose.

- have liver problems. You may need to be checked for liver problems while you take XELODA.

- take the vitamin folic acid. It may affect how XELODA works.

How should I take XELODA?

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

- Take the tablets in the combination prescribed by your doctor for your **morning and evening** doses.

- Take the tablets **within 30 minutes after the end of a meal** (breakfast and dinner).

- **Swallow XELODA with water.**

- If you miss a dose of XELODA, do <u>not</u> take the missed dose at all and do <u>not</u> double the next one. Instead, continue your regular dosing schedule and check with your doctor.

- It is recommended that XELODA be taken for 14 days followed by a 7-day rest period (no drug), given as a 21-day cycle. Your doctor will tell you how many cycles of treatment you will need.

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- In case of accidental swallowing, or if you suspect that too much medicine has been taken, contact your doctor or local poison control center or emergency room **right away**.

What should I avoid while taking XELODA?

- Women should not become pregnant while taking XELODA. XELODA may harm your unborn child. Use effective birth control while taking XELODA. Tell your doctor if you become pregnant.

- Men should practice birth control measures while taking XELODA.

- Do not breast-feed. XELODA may pass through your milk and harm the baby.

What are the most common side effects of XELODA?

The most common side effects of XELODA are:

- diarrhea, nausea, vomiting, stomatitis (sores in mouth and throat), abdominal (stomach area) pain, upset stomach, constipation, loss of appetite, and dehydration (too much water loss from the body). These side effects are more common in patients age 80 and older.

- hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb, painful, swollen or red), rash, dry, itchy or discolored skin, nail problems, and hair loss.

- tiredness, weakness, dizziness, headache, fever, pain (including chest, back, joint, and muscle pain), trouble sleeping, and taste problems.

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

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

Do not continue to take XELODA until you have talked to your doctor if you have the side effects listed below, or other side effects that concern you. Your doctor can help reduce the chance that the side effects will continue or become serious. Your doctor may tell you to decrease the dose or stop XELODA treatment for a while.

Contact your doctor right away if you have:

- ***Diarrhea:*** if you have more than 4 bowel movements each day or any diarrhea at night

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- ***Vomiting:*** if you vomit more than once in a 24-hour time period
- ***Nausea:*** if you lose your appetite, and the amount of food you eat each day is much less than usual
- ***Stomatitis:*** if you have pain, redness, swelling or sores in your mouth
- ***Hand-and-Foot Syndrome:*** if you have pain and swelling or redness of your hands or feet that prevents normal activity
- ***Fever or Infection:*** if you have a temperature of 100.5°F or greater, or other signs of infection

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

How should I store and use XELODA?

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

General advice about prescription medicines:

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

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

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XELODA® (capecitabine)

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