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, 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**

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.0)	10/2014
Warnings and Precautions (5.1, 5.2, 5.5, and 5.7)	10/2014

---------- 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/m^2 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/m^2 twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 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 ----------
- **Coagulopathy**: May result in bleeding, death. Monitor anticoagulant response (e.g., INR) and adjust anticoagulant dose accordingly. (5.1)
- **Diarrhea**: May be severe. Interrupt XELODA treatment immediately until diarrhea resolves or decreases to grade 1. Recommend standard antidiarrheal treatments. (5.2)
- **Cardiotoxicity**: Common in patients with a prior history of coronary artery disease. (5.3)
- **Dehydration and Renal Failure**: Interrupt XELODA treatment until dehydration is corrected. Potential risk of acute renal failure secondary to dehydration. Monitor and correct dehydration. (5.5).
- **Pregnancy**: Can cause fetal harm. Advise women of the potential risk to the fetus. (5.6, 8.1)
- **Mucocutaneous and Dermatologic Toxicity**: Severe mucocutaneous reactions, Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), have been reported. XELODA should be permanently discontinued in patients who experience a severe mucocutaneous reaction during treatment. XELODA may induce hand-and-foot syndrome. Interrupt XELODA treatment until the hand-and-foot syndrome event resolves or decreases in intensity. (5.7)
- **Hyperbilirubinemia**: 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 10^9/L or thrombocyte counts <100 x 10^9/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

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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/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.

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2 DOSAGE AND ADMINISTRATION

XELODA tablets should be swallowed whole with water within 30 minutes after a meal. Do not crush or cut XELODA tablets. XELODA dose is calculated according to body surface area.

2.1 Standard Starting Dose

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

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 (see **Table 1**).

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

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

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

In Combination With Docetaxel (Metastatic Breast Cancer)

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 75 mg/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 1** displays the total daily dose of XELODA by body surface area and the number of tablets to be taken at each dose.

2.2 Dose Management Guidelines

General

XELODA dosage may need to be individualized to optimize patient management. Patients should be carefully monitored for toxicity and doses of XELODA should be modified as necessary to accommodate individual patient tolerance to treatment *[see Clinical Studies (14)]*. 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

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increased at a later time. Doses of XELODA omitted for toxicity are not replaced or restored; instead the patient should resume the planned treatment cycles.

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

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

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

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%

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

In Combination With Docetaxel (Metastatic Breast Cancer)

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

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

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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/m2 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	-	-

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

2.3 Adjustment of Starting Dose in Special Populations

Renal Impairment

No adjustment to the starting dose of XELODA is recommended in patients with mild renal impairment (creatinine clearance = 51 to 80 mL/min [Cockroft and Gault, as shown below]). In patients with moderate renal impairment (baseline creatinine clearance = 30 to 50 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 Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*. Subsequent dose adjustment is recommended as outlined in **Table 2** and **Table 3** (depending on the regimen) if a patient develops a grade 2 to 4 adverse event *[see Warnings and Precautions (5.5)]*. The starting dose adjustment recommendations for patients with moderate renal impairment apply to both XELODA monotherapy and XELODA in combination use with docetaxel.

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.

3 DOSAGE FORMS AND STRENGTHS

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

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4 CONTRAINDICATIONS

4.1 Dihydropyrimidine Dehydrogenase (DPD) Deficiency

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

4.2 Severe Renal Impairment

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

4.3 Hypersensitivity

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.

5 WARNINGS AND PRECAUTIONS

General

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

5.1 Coagulopathy

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 Drug Interactions (7.1)]*.

5.2 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 875 patients with either metastatic breast or colorectal cancer who received XELODA monotherapy, 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 *[see Dosage and Administration (2.2)]*. Standard antidiarrheal treatments (eg, loperamide) are recommended.

Necrotizing enterocolitis (typhlitis) has been reported.

5.3 Cardiotoxicity

The cardiotoxicity observed with XELODA includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and

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cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

5.4 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.

5.5 Dehydration and Renal Failure

Dehydration has been observed and may cause acute renal failure which can be fatal. Patients with pre-existing compromised renal function or who are receiving concomitant XELODA with known nephrotoxic agents are at higher risk. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated. Monitor patients when XELODA is administered to prevent and correct dehydration at the onset. If grade 2 (or higher) dehydration occurs, XELODA treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications should be applied for the precipitating adverse event as necessary [*see Dosage and Administration (2.2)*].

Patients with moderate renal impairment at baseline require dose reduction *[see Dosage and Administration (2.3)]*. Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse reactions. 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 2** *[see Dosage and Administration (2.2), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

5.6 Pregnancy

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

5.7 Mucocutaneous and Dermatologic Toxicity

Severe mucocutaneous reactions, some with fatal outcome, such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN) can occur in patients treated with XELODA [*see Adverse Reactions (6.4)*]. XELODA should be permanently discontinued in patients who experience a severe mucocutaneous reaction possibly attributable to XELODA treatment.

Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity. Median time to onset was 79 days (range from 11 to 360 days) with a severity range of grades 1 to 3 for patients receiving XELODA monotherapy in the metastatic setting. 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

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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. Following grade 3 hand-and-foot syndrome, subsequent doses of XELODA should be decreased *[see Dosage and Administration (2.2)]*.

5.8 Hyperbilirubinemia

In 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, grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) of patients and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 3.9% (n=34) of patients. 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).

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

5.9 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.

Patients with baseline neutrophil counts of <1.5 x 10^9/L and/or thrombocyte counts of <100 x 10^9/L should not be treated with XELODA. If unscheduled laboratory assessments during a

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treatment cycle show grade 3 or 4 hematologic toxicity, treatment with XELODA should be interrupted.

5.10 Geriatric Patients

Patients ≥80 years old may experience a greater incidence of grade 3 or 4 adverse reactions. In 875 patients with either metastatic breast or colorectal cancer who received XELODA monotherapy, 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 reactions, treatment-related serious adverse reactions, withdrawals due to adverse reactions, treatment discontinuations due to adverse reactions and treatment discontinuations within the first two treatment cycles was higher than in the <60 years of age patient group.

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

5.11 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 Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

5.12 Combination With Other Drugs

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

6 ADVERSE REACTIONS

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

6.1 Adjuvant Colon Cancer

Table 4 shows the adverse reactions occurring in ≥5% of patients from one phase 3 trial in patients with Dukes' C colon cancer who received at least one dose of study medication and had at least one safety assessment. A total of 995 patients were treated with 1250 mg/m^2 twice a day of XELODA administered for 2 weeks followed by a 1-week rest period, and 974 patients were

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administered 5-FU and leucovorin (20 mg/m^2 leucovorin IV followed by 425 mg/m^2 IV bolus 5-FU on days 1-5 every 28 days). The median duration of treatment was 164 days for capecitabine-treated patients and 145 days for 5-FU/LV-treated patients. A total of 112 (11%) and 73 (7%) capecitabine and 5-FU/LV-treated patients, respectively, discontinued treatment because of adverse reactions. A total of 18 deaths due to all causes occurred either on study or within 28 days of receiving study drug: 8 (0.8%) patients randomized to XELODA and 10 (1.0%) randomized to 5-FU/LV.

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

Table 4 Percent Incidence of Adverse Reactions Reported in ≥5% of Patients Treated With XELODA or 5-FU/LV for Colon Cancer in the Adjuvant Setting (Safety Population)

	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**
Gastrointestinal Disorders				
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	-
Skin and Subcutaneous Tissue Disorders				
Hand-and-Foot Syndrome	60	17	9	<1
Alopecia	6	-	22	<1
Rash	7	-	8	-
Erythema	6	1	5	<1
General Disorders and Administration Site Conditions				
Fatigue	16	<1	16	1
Pyrexia	7	<1	9	<1
Asthenia	10	<1	10	1
Lethargy	10	<1	9	<1

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	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**
Nervous System Disorders				
Dizziness	6	<1	6	-
Headache	5	<1	6	<1
Dysgeusia	6	-	9	-
Metabolism and Nutrition Disorders				
Anorexia	9	<1	11	<1
Eye Disorders				
Conjunctivitis	5	<1	6	<1
Blood and Lymphatic System Disorders				
Neutropenia	2	<1	8	5
Respiratory Thoracic and Mediastinal Disorders				
Epistaxis	2	-	5	-

Table 5 Percent Incidence of Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Patients Receiving XELODA Monotherapy for Adjuvant Treatment of Colon Cancer (Safety Population)

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

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

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

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6.2 Metastatic Colorectal Cancer

Monotherapy

Table 6 shows the adverse reactions occurring in ≥5% of patients from pooling the two phase 3 trials in first line metastatic colorectal cancer. A total of 596 patients with metastatic colorectal cancer were treated with 1250 mg/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 reactions/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.

Table 6 Pooled Phase 3 Colorectal Trials: Percent Incidence 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

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Adverse Event	XELODA (n=596)			5-FU/LV (n=593)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
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	–	–
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

6.3 Breast Cancer

In Combination with Docetaxel

The following data are shown for the combination study with XELODA and docetaxel in patients with metastatic breast cancer in **Table 7** and **Table 8**. 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

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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 reactions. The percentage of patients requiring dose reductions due to adverse reactions was 65% in the combination arm and 36% in the monotherapy arm. The percentage of patients requiring treatment interruptions due to adverse reactions 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 7 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/bid With Docetaxel 75 mg/m^2/3 weeks (n=251)**			**Docetaxel 100 mg/m^2/3 weeks (n=255)**		
	Total %	**Grade 3 %**	**Grade 4 %**	**Total %**	**Grade 3 %**	**Grade 4 %**
Number of Patients With at Least One Adverse Event	99	76.5	29.1	97	57.6	31.8
Body System/Adverse Event						
GI						
Diarrhea	67	14	<1	48	5	<1
Stomatitis	67	17	<1	43	5	–
Nausea	45	7	–	36	2	–
Vomiting	35	4	1	24	2	–
Constipation	20	2	–	18	–	–
Abdominal Pain	30	<3	<1	24	2	–
Dyspepsia	14	–	–	8	1	–
Dry Mouth	6	<1	–	5	–	–
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/m^2/bid With Docetaxel 75 mg/m^2/3 weeks (n=251)			Docetaxel 100 mg/m^2/3 weeks (n=255)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
General						
Pyrexia	28	2	–	34	2	–
Asthenia	26	4	<1	25	6	–
Fatigue	22	4	–	27	6	–
Weakness	16	2	–	11	2	–
Pain in Limb	13	<1	–	13	2	–
Lethargy	7	–	–	6	2	–
Pain	7	<1	–	5	1	–
Chest Pain (non-cardiac)	4	<1	–	6	2	–
Influenza-like Illness	5	–	–	5	–	–
Neurological						
Taste Disturbance	16	<1	–	14	<1	–
Headache	15	3	–	15	2	–
Paresthesia	12	<1	–	16	1	–
Dizziness	12	–	–	8	<1	–
Insomnia	8	–	–	10	<1	–
Peripheral Neuropathy	6	–	–	10	1	–
Hypoaesthesia	4	<1	–	8	<1	–
Metabolism						
Anorexia	13	1	–	11	<1	–
Appetite Decreased	10	–	–	5	–	–
Weight Decreased	7	–	–	5	–	–
Dehydration	10	2	–	7	<1	<1
Eye						
Lacrimation Increased	12	–	–	7	<1	–
Conjunctivitis	5	–	–	4	–	–
Eye Irritation	5	–	–	1	–	–
Musculoskeletal						
Arthralgia	15	2	–	24	3	–
Myalgia	15	2	–	25	2	–
Back Pain	12	<1	–	11	3	–
Bone Pain	8	<1	–	10	2	–
Cardiac						
Edema	33	<2	–	34	<3	1
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	–

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Adverse Event	XELODA 1250 mg/m^2/bid With Docetaxel 75 mg/m^2/3 weeks (n=251)			Docetaxel 100 mg/m^2/3 weeks (n=255)		
	Total %	Grade 3 %	Grade 4 %	Total %	Grade 3 %	Grade 4 %
Vascular						
Flushing	5	–	–	5	–	–
Lymphoedema	3	<1	–	5	1	–
Psychiatric						
Depression	5	–	–	5	1	–

– Not observed
NA = Not Applicable

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

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 reactions/intercurrent illness.

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Table 9 **Percent Incidence of Adverse Reactions 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

6.4 Clinically Relevant Adverse Events in <5% of Patients

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

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

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

Skin & Subcutan.: 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 & Lymphatic: leukopenia (0.2%), coagulation disorder (0.1%), bone marrow depression (0.1%), idiopathic thrombocytopenia purpura (1.0%), pancytopenia (0.1%)

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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
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, lacrimal duct stenosis, acute renal failure secondary to dehydration including fatal outcome [*see Warnings and Precautions (5.5)*], cutaneous lupus erythematosus, corneal disorders including keratitis, severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN) [*see Warnings and Precautions (5.7)*]

XELODA In Combination With Docetaxel (Metastatic Breast Cancer)

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

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

Anticoagulants

Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon *[see Boxed Warning]*. 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 *[see Clinical Pharmacology (12.3)]*. 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.

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 (2.2)]*. Postmarketing reports indicate that some patients receiving XELODA and phenytoin had toxicity associated with

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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.

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.

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.

7.2 Drug-Food Interaction

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Category D

XELODA can cause fetal harm when administered 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 of XELODA in pregnant women. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving XELODA, the patient should be apprised of the potential hazard to the fetus. Women should be advised to avoid becoming pregnant while receiving treatment with XELODA *[see Warnings and Precautions (5.6)]*.

8.3 Nursing Mothers

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

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8.4 Pediatric Use

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

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

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

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

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

8.5 Geriatric Use

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

8.6 Hepatic Insufficiency

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

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8.7 Renal Insufficiency

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

10 OVERDOSAGE

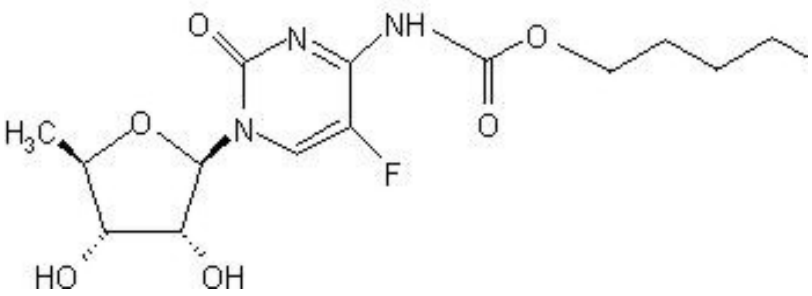
The manifestations of acute overdose would include nausea, vomiting, diarrhea, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of overdose should include customary supportive medical interventions aimed at correcting the presenting clinical manifestations. Although 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).

11 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 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enzymes convert capecitabine to 5-fluorouracil (5-FU) *in vivo*. Both normal and tumor cells metabolize 5-FU to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine

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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. 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.

12.3 Pharmacokinetics

Absorption

Following oral administration of 1255 mg/m^2 BID to cancer patients, 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 Warnings and Precautions (5), Dosage and Administration (2), and Drug-Food Interaction (7.2)]*.

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 interpatient variability in the C_{max} and AUC of 5-FU was greater than 85%.

Distribution

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

Bioactivation and Metabolism

Capecitabine is extensively metabolized enzymatically to 5-FU. 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'-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. 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.

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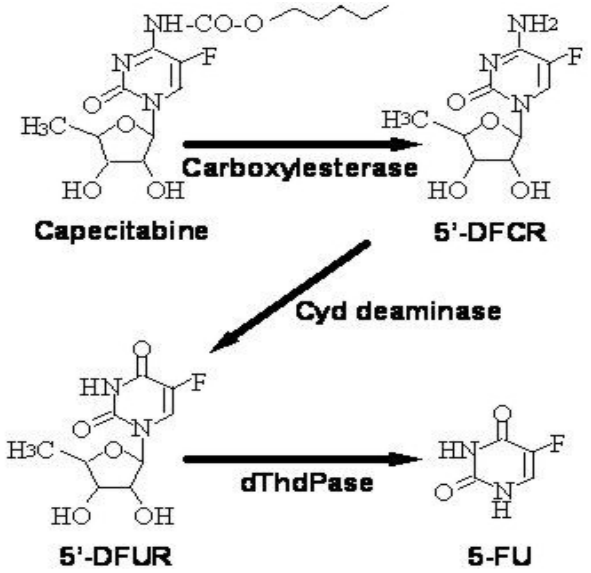
Metabolic Pathway of capecitabine to 5-FU



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.

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

Excretion

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. The elimination half-life of both parent capecitabine and 5-FU was about 0.75 hour.

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

A population analysis of pooled data from the two large controlled studies in patients with metastatic 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 Precautions (5.11) and Dosage and Administration (2.3)]*.

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

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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).

Effect of 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 Warnings and Precautions (5.11) and Use in Special Populations (8.6)]*.

Effect of 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 Dosage and Administration (2.3), Contraindications (4.2), Warnings and Precautions (5.5), and Use in Special Populations (8.7)]*.

Effect of Capecitabine on the Pharmacokinetics of Warfarin

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 Drug Interactions (7.1)]*.

Effect of Antacids on the Pharmacokinetics of Capecitabine

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.

Effect of Capecitabine on the Pharmacokinetics of Docetaxel and Vice Versa

A Phase 1 study evaluated 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.

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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 female mice, oral capecitabine doses of 760 mg/kg/day (about 2300 mg/m^2/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.

14 CLINICAL STUDIES

14.1 Adjuvant Colon Cancer

A multicenter randomized, controlled phase 3 clinical trial in patients with Dukes' C colon cancer (X-ACT) provided data concerning the use of XELODA for the adjuvant treatment of patients with colon cancer. The primary objective of the study was to compare disease-free survival (DFS) in patients receiving XELODA to those receiving IV 5-FU/LV alone. In this trial, 1987 patients were randomized either to treatment with XELODA 1250 mg/m^2 orally twice daily for 2 weeks followed by a 1-week rest period, given as 3-week cycles for a total of 8 cycles (24 weeks) or IV bolus 5-FU 425 mg/m^2 and 20 mg/m^2 IV leucovorin on days 1 to 5, given as 4-week cycles for a total of 6 cycles (24 weeks). Patients in the study were required to be between 18 and 75 years of age with histologically-confirmed Dukes' stage C colon cancer with at least one positive lymph node and to have undergone (within 8 weeks prior to randomization) complete resection of the primary tumor without macroscopic or microscopic evidence of remaining tumor. Patients were also required to have no prior cytotoxic chemotherapy or immunotherapy (except steroids), and have an ECOG performance status of 0 or 1 (KPS ≥ 70%), ANC ≥ 1.5x10^9/L, platelets ≥ 100x10^9/L, serum creatinine ≤ 1.5 ULN, total bilirubin ≤ 1.5 ULN, AST/ALT ≤ 2.5 ULN and CEA within normal limits at time of randomization.

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

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Table 10 Baseline Demographics

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

All patients with normal renal function or mild renal impairment began treatment at the full starting dose of 1250 mg/m^2 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**).

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

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

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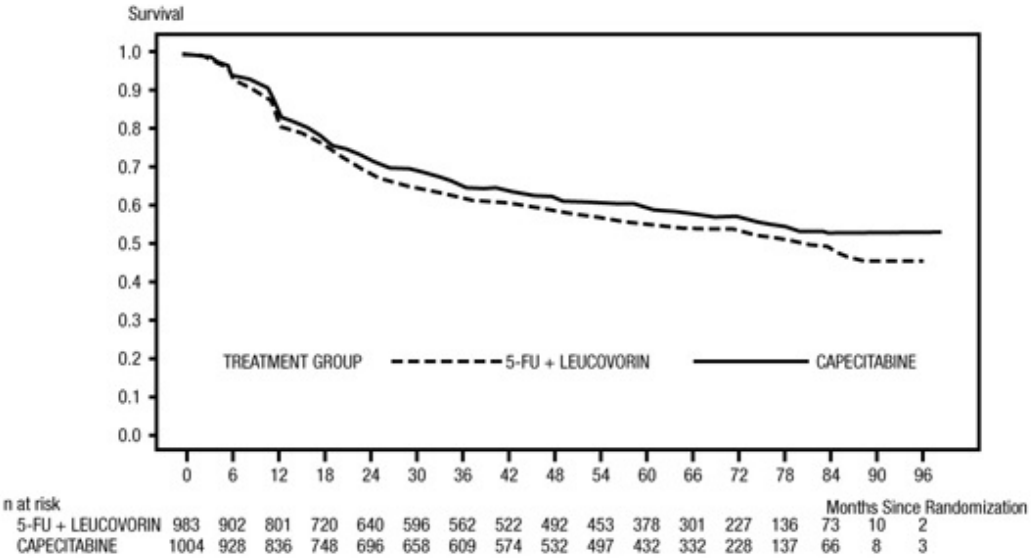
ratio for XELODA compared to 5-FU/LV with respect to overall survival was 0.86 (95% C.I. 0.74 – 1.01). The 5-year overall survival rates were 71.4% for XELODA and 68.4% for 5-FU/LV (see **Figure 2)**.

Table 12 Efficacy of XELODA vs 5-FU/LV in Adjuvant Treatment of Colon Cancer[a]

All Randomized Population	**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)	0.88 (0.77 - 1.01)	
p-value[c]	p = 0.068	

[a]Approximately 93.4% had 5-year DFS information
[b]Based on Kaplan-Meier estimates
[c]Test of superiority of XELODA vs 5-FU/LV (Wald chi-square test)

Figure 1 Kaplan-Meier Estimates of Disease-Free Survival (All Randomized Population)[a]



[a]XELODA has been demonstrated to be non-inferior to 5-FU/LV.

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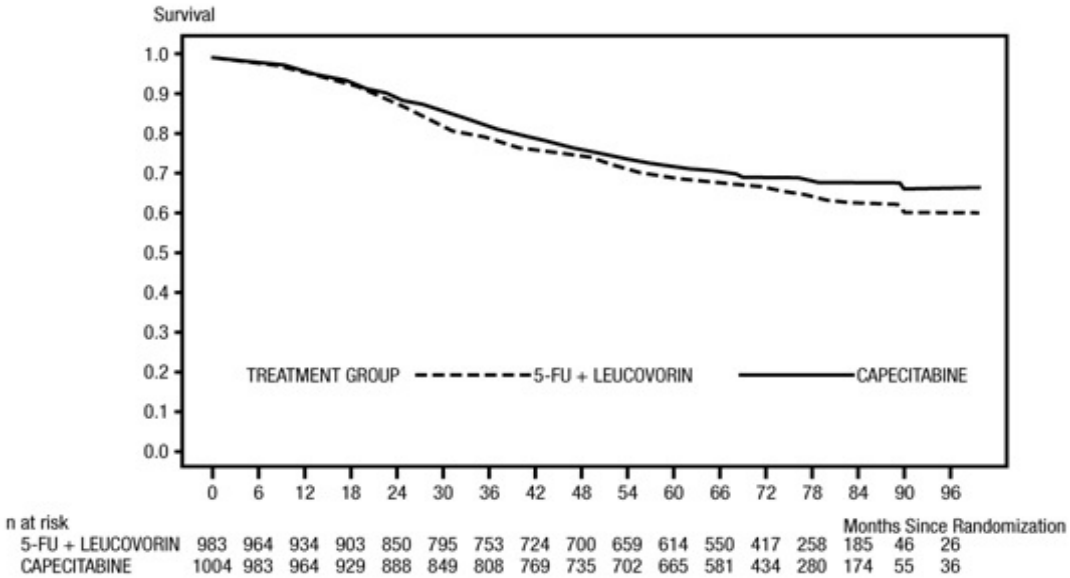
Figure 2 Kaplan-Meier Estimates of Overall Survival (All Randomized Population)



14.2 Metastatic Colorectal Cancer

General

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.

Monotherapy

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).

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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 13**.

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) 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)

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

Table 14 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, 95% C.I.)	 380 (321-434)	 407 (366-446)
Hazard Ratio (XELODA/5-FU/LV) 95% C.I. for Hazard Ratio	1.00 (0.84-1.18)	

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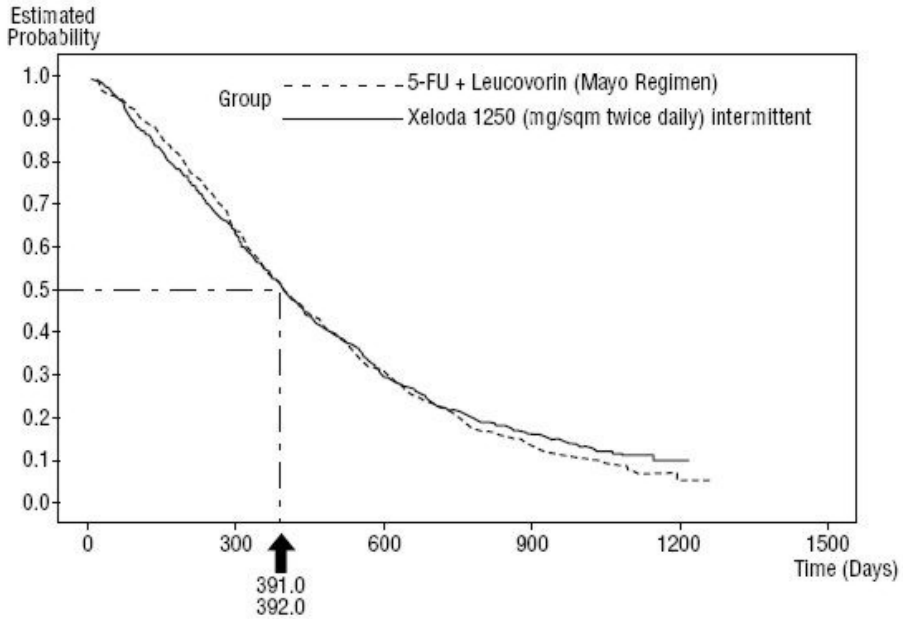
Table 15 Efficacy of XELODA vs 5-FU/LV in Colorectal Cancer (Study 2)

	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)	

Figure 3 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

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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 **Table 14**, **Table 15**, and **Figure 3**).

14.3 Breast Cancer

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

In Combination With Docetaxel

The dose of XELODA used in the 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 16**.

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Table 16 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

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 17**, **Figure 4**, and **Figure 5**.

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Table 17 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

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

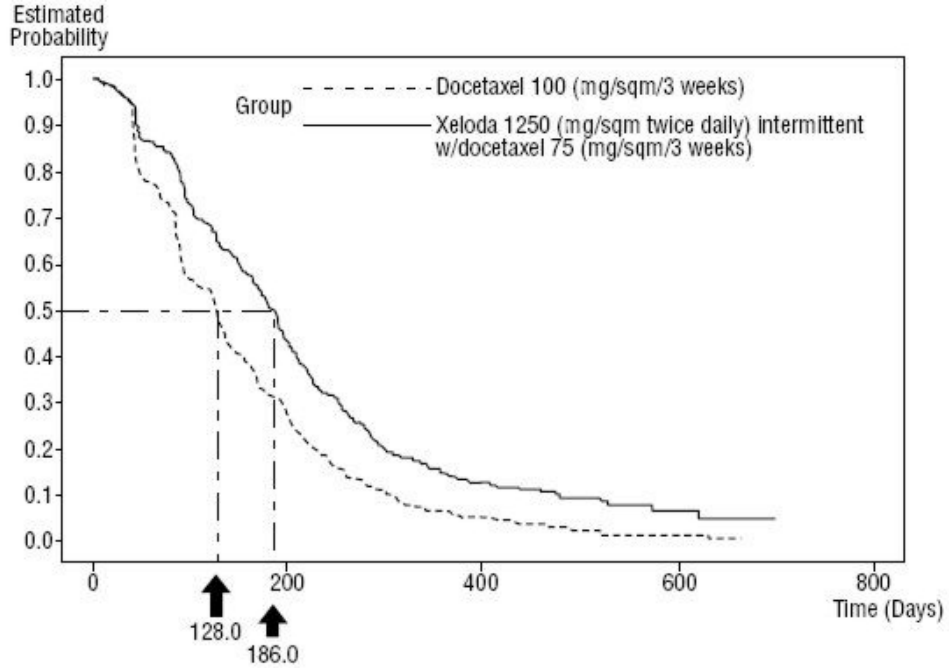

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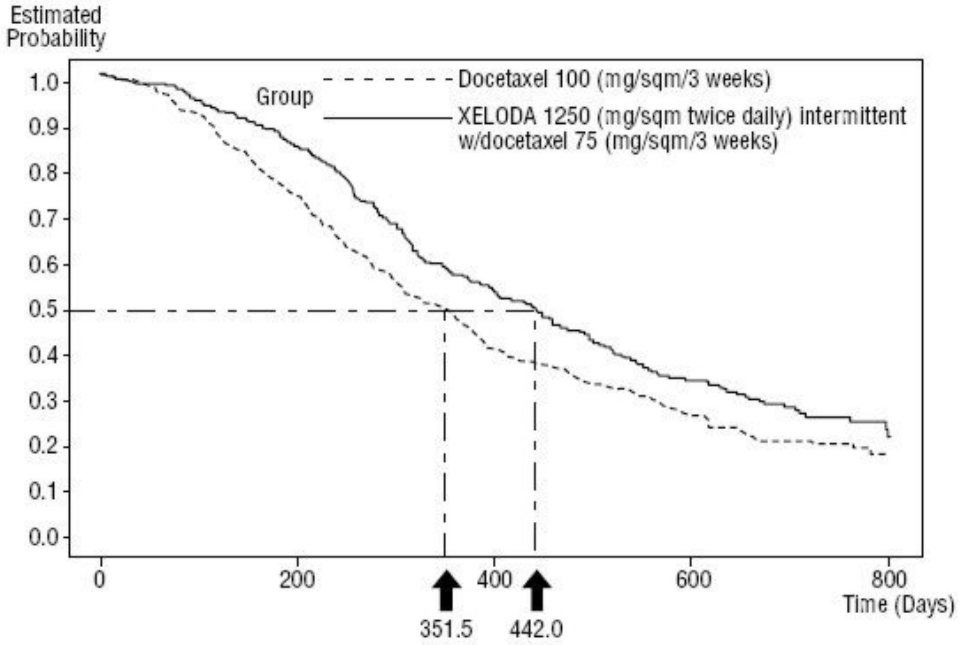
Figure 5 Kaplan-Meier Estimates of Survival XELODA and Docetaxel vs Docetaxel



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 18**. 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.

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Table 18 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

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

Table 19 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

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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 18**). The median time to progression was 90 days and the median survival was 306 days.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

150 mg

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

500 mg

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

Storage and Handling

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

Care should be exercised in the handling of XELODA. XELODA tablets should not be cut or crushed. Procedures for the proper handling and disposal of anticancer drugs should be considered. Any unused product should be disposed of in accordance with local requirements, or drug take back programs. Several guidelines on the subject have been published.[1-4]

17 PATIENT COUNSELING INFORMATION

Information for Patients (see FDA-approved Patient Labeling)

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

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made aware that patient-specific dose adaptations during therapy are expected and necessary *[see Dosage and Administration (2.2)]*. As described below, patients taking XELODA should be informed of the need to interrupt treatment and to call their physician immediately if moderate or severe toxicity occurs. Patients should be encouraged to recognize the common grade 2 toxicities associated with XELODA treatment See FDA-approved patient labeling (Patient Information).

Diarrhea

Patients experiencing grade 2 diarrhea (an increase of 4 to 6 stools/day or nocturnal stools) or greater or experiencing severe bloody diarrhea with severe abdominal pain and fever should be instructed to stop taking XELODA and to call their physician immediately. Standard antidiarrheal treatments (eg, loperamide) are recommended.

Dehydration

Patients experiencing grade 2 or higher dehydration should be instructed to stop taking XELODA immediately and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled.

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.

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. Initiation of symptomatic treatment is recommended.

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 and to call their physician. Initiation of symptomatic treatment is recommended.

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 immediately.

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1 DNA Way
South San Francisco, CA 94080-4990

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Patient Information

XELODA® (zeh-LOE-duh)

(capecitabine) Tablets, Film Coated

What is the most important information I should know about XELODA?

XELODA can cause serious side effects, including:

- XELODA can interact with blood thinner medicines, such as warfarin (COUMADIN®). Taking XELODA with these medicines can cause changes in how fast your blood clots, and can cause bleeding that can lead to death. This can happen as soon as a few days after you start taking XELODA, or later during treatment, and possibly even within 1 month after you stop taking XELODA. Your risk may be higher because you have cancer, and if you are over 60 years of age.
  - Before taking XELODA, tell your doctor if you are taking warfarin (COUMADIN) or another blood thinner–medicine.
  - If you take warfarin (COUMADIN) or another blood thinner that is like warfarin (COUMADIN) during treatment with XELODA, your doctor should do blood tests often, to check how fast your blood clots during and after you stop treatment with XELODA. Your doctor may change your dose of the blood thinner medicine if needed.

See **"What are the possible side effects of XELODA?"** for more information about side effects.

What is XELODA?

XELODA is a prescription medicine used to treat people with:

- cancer of the colon that has spread to lymph nodes in the area close to the colon (Dukes' C stage), after they have surgery.
- cancer of the colon or rectum (colorectal) that has spread to other parts of the body (metastatic).
- breast cancer that has spread to other parts of the body (metastatic) together with another medicine called docetaxel after treatment with certain other anti-cancer medicines have not worked.
- breast cancer that has spread to other parts of the body and has not improved after treatment with paclitaxel and certain other anti-cancer medicines, or who cannot receive any more treatment with certain anti-cancer medicines.

It is not known if XELODA is safe and effective in children.

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Who should not take XELODA?

Do not take XELODA if you:

- have been told that you lack the enzyme DPD (dihydropyrimidine dehydrogenase).
- have severe kidney problems.
- are allergic to capecitabine, 5-fluorouracil, or any of the ingredients in XELODA. See the end of this leaflet for a complete list of ingredients in XELODA.

Talk to your doctor before taking XELODA if you are not sure if you have any of the conditions listed above.

What should I tell my doctor before taking XELODA?

See "**What is the most important information I should know about XELODA**?".

Before you take XELODA, tell your doctor if you:

- have had heart problems.
- have kidney or liver problems.
- have any other medical conditions.
- are pregnant or plan to become pregnant. XELODA can harm your unborn baby. You should not become pregnant during treatment with XELODA. Talk to your doctor about birth control choices that may be right for you during treatment with XELODA.
- are breastfeeding or plan to breastfeed. It is not known if XELODA passes into your breast milk. You and your doctor should decide if you will take XELODA or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XELODA may affect the way other medicines work, and other medicines may affect the way XELODA works.

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take XELODA?

- Take XELODA exactly as your doctor tells you to take it.
- Your doctor will tell you how much XELODA to take and when to take it.
- Take XELODA 2 times a day, 1 time in the morning and 1 time in the evening.
- Take XELODA within 30 minutes after finishing a meal. Swallow XELODA tablets whole with water. Do not crush or cut XELODA tablets.

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- Ask your healthcare provider or pharmacist how to safely throw away any unused XELODA.
- If you have side effects with XELODA, if needed your doctor may decide to:
  - change your dose of XELODA
  - treat you with XELODA less often
  - tell you to stop taking XELODA until certain side effects get better or go away
  - stop your treatment with XELODA if you have certain side effects and they are severe
- If you take too much XELODA, call your doctor or go to the nearest emergency room right away.

What are the possible side effects of XELODA?

XELODA may cause serious side effects including:

See **"What is the most important information I should know about XELODA?".**

- **diarrhea.** Diarrhea is common with XELODA and can sometimes be severe. Stop taking XELODA and call your doctor right away if the number of bowel movements you have in a day increases by 4 or more than is usual for you. Ask your doctor about what medicines you can take to treat your diarrhea. If you have severe bloody diarrhea with severe abdominal pain and fever, call your doctor or go to the nearest emergency room right away.
- **heart problems.** XELODA can cause heart problems including: heart attack and decreased blood flow to the heart, chest pain, irregular heartbeats, changes in the electrical activity of your heart seen on an electrocardiogram (ECG), problems with your heart muscle, heart failure, and sudden death. Stop taking XELODA and call your doctor right away if you get any of the following symptoms:
  - chest pain
  - shortness of breath
  - feeling faint
  - irregular heartbeats or skipping beats
  - sudden weight gain
  - swollen ankles or legs
- **unexplained tiredness**
- **loss of too much body fluid (dehydration) and kidney failure.** Dehydration can happen with XELODA and may cause sudden kidney failure that

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can lead to death. You are at higher risk if you have kidney problems before taking XELODA and also take other medicines that can cause kidney problems.

Nausea, and vomiting are common with XELODA. If you lose your appetite, feel weak, and have nausea, vomiting, or diarrhea, you can quickly become dehydrated.

Stop taking XELODA and call your doctor right away if you:

- vomit 2 or more times in a day.
- are only able to eat or drink a little now and then, or not at all due to nausea.
- have diarrhea. See “diarrhea” above.

- **serious skin and mouth reactions.**
  - XELODA can cause serious skin reactions that may lead to death. Tell your doctor right away if you develop a skin rash, blisters and peeling of your skin. Your doctor may tell you to stop taking XELODA if you have a serious skin reaction. Do not take XELODA again if this happens.
  - XELODA can also cause “hand and foot syndrome.” Hand and foot syndrome is common with XELODA and can cause you to have numbness and changes in sensation in your hands and feet, or cause redness, pain, swelling of your hands and feet. Stop taking XELODA and call your doctor right away if you have any of these symptoms and you are not able to do your usual activities.
  - you may get sores in your mouth or on your tongue when taking XELODA. Stop taking XELODA and call your doctor if you get painful redness, swelling, or ulcers in your mouth and tongue, or if you are having problems eating. Tell your doctor if you have any side effect that bothers you or that does not go away.
- **increased level of bilirubin in your blood and liver problems.** Increased bilirubin in your blood is common with XELODA. Your doctor will check you for these problems during treatment with XELODA.
- **decreased white blood cells, platelets, and red blood cell counts.** Your doctor will do blood tests during treatment with XELODA to check your blood cell counts.

  If your white blood cell count is very low, you are at increased risk for infection. Call your doctor right away if you develop a fever of 100.5°F or greater or have other signs and symptoms of infection.

People 80 years of age or older may be more likely to develop severe or serious side effects with XELODA.

The most common side effects of XELODA include:

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- diarrhea
- hand and foot syndrome
- nausea
- vomiting
- stomach-area (abdominal) pain
- tiredness
- weakness
- increased amounts of red blood cell breakdown products (bilirubin) in your blood

These are not all the possible side effects of XELODA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XELODA?

- Store XELODA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep XELODA in a tightly closed container.
- Keep XELODA and all medicines out of the reach of children.

General information about the safe and effective use of XELODA.

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.

You can ask your pharmacist or doctor for information about XELODA that is written for health professionals.

For more information, go to http://www.gene.com/patients/medicines/xeloda or call 1-877-436-3683.

What are the ingredients in XELODA?

Active ingredient: capecitabine

Inactive ingredients: 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.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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