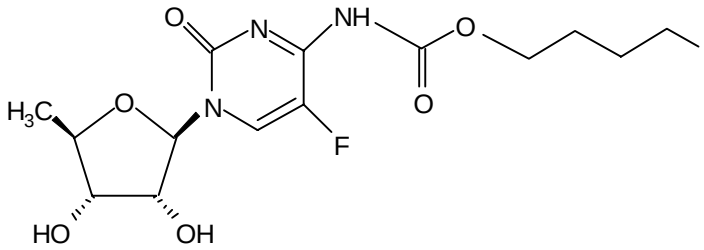
Roche

XELODA®
(capecitabine)
TABLETS

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.

CLINICAL PHARMACOLOGY: Capecitabine is relatively non-cytotoxic in vitro. This drug is enzymatically converted to 5-fluorouracil (5-FU) in vivo.

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

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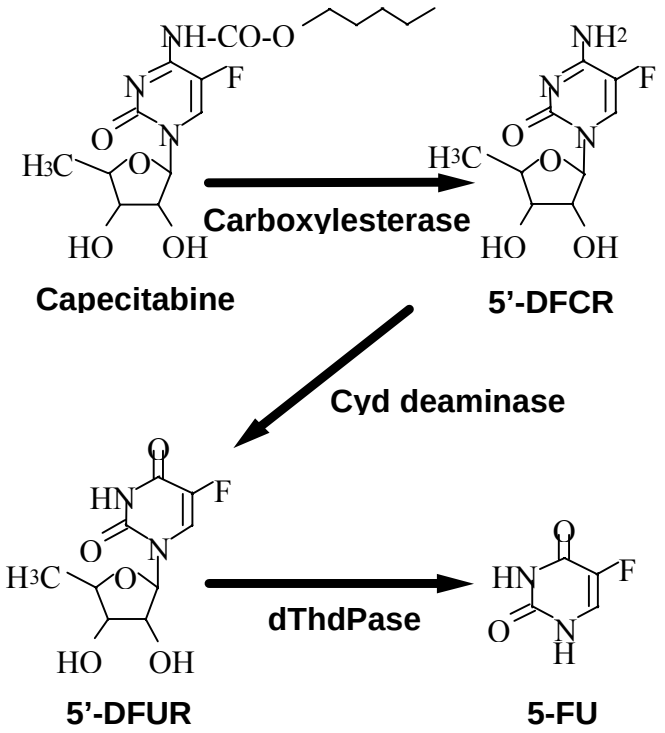
Metabolic Pathway of capecitabine to 5-FU



Mechanism of Action: Both normal and tumor cells metabolize 5-FU to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N^{5-10}-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from uracil. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

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

Human Pharmacokinetics: The pharmacokinetics of XELODA and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m^2/day. Over this range, the pharmacokinetics of capecitabine and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14

than on day 1. The elimination half-life of both parent capecitabine and 5-FU was about ¾ of an hour. The inter-patient variability in the C_{max} and AUC of 5-FU was greater than 85%.

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

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

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

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.

Special Populations:

Age, Gender and Ethnicity: No formal studies were conducted to examine the effect of age or gender or ethnicity on the pharmacokinetics of capecitabine and its metabolites.

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 capecitabine. 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 was not affected. In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when XELODA is administered. The effect of severe hepatic dysfunction on XELODA is not known (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions:

Drugs Metabolized by Cytochrome P450 Enzymes: In vitro enzymatic studies with human liver microsomes indicated that capecitabine and 5'-DFUR had no inhibitory effects on substrates of cytochrome P450 for the major isoenzymes such as 1A2, 2A6, 3A4, 2C9, 2C19, 2D6, and 2E1, suggesting a low likelihood of interactions with drugs metabolized by cytochrome P450

enzymes.

Antacid: When Maalox®* (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after capecitabine (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 capecitabine.

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

CLINICAL STUDIES: In a phase 1 study with XELODA in patients with solid tumors, the maximum tolerated dose as a single agent was 3000 mg/m^2 when administered daily for 2 weeks, followed by a 1-week rest period. The dose-limiting toxicities were diarrhea and leukopenia.

Breast Carcinoma: The antitumor activity of XELODA 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 daily dose of 2510 mg/m^2 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 the table below. 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 1. Baseline Demographics and Clinical Characteristics

	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 the table below.

Table 2. Response Rates in Doubly-Resistant Patients

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

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

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

INDICATIONS AND USAGE: XELODA is indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated, eg, patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen.

This indication is based on demonstration of a response rate. No results are available from controlled trials that demonstrate a clinical benefit resulting from treatment, such as improvement in disease-related symptoms, disease progression, or survival.

CONTRAINDICATIONS: XELODA is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil.

XELODA is also contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).

WARNINGS: *Renal Insufficiency:* In patients with moderate renal impairment (creatinine clearance 30-50 mL/min [Cockroft and Gault]) at baseline, a dose reduction to 75% of the XELODA starting dose is recommended. In patients with mild renal impairment (creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. (see DOSAGE AND ADMINISTRATION). Careful monitoring and prompt treatment interruption is recommended if

the patient develops a grade 2, 3, or 4 adverse event with subsequent dose adjustments as outlined in the table in DOSAGE AND ADMINISTRATION.

Coagulopathy: Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating XELODA therapy and, in a few cases, within one month after stopping XELODA. These events occurred in patients with and without liver metastases. Patients taking coumarin-derivative anticoagulants concomitantly with XELODA should be monitored regularly for alterations in their coagulation parameters (PT or INR) (see PRECAUTIONS: *Drug-Drug Interactions*).

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. The median time to first occurrence of grade 2-4 diarrhea was 31 days (range from 1 to 322 days). National Cancer Institute of Canada (NCIC) grade 2 diarrhea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an increase of ≥10 stools/day or grossly bloody diarrhea or the need for parenteral support. If grade 2, 3 or 4 diarrhea occurs, administration of XELODA should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1. Following grade 3 or 4 diarrhea, subsequent doses of XELODA should be decreased (see DOSAGE AND ADMINISTRATION). Standard antidiarrheal treatments (eg, loperamide) are recommended.

Necrotizing enterocolitis (typhlitis) has been reported.

Geriatric Patients (gastrointestinal toxicity): Patients ≥80 years old may experience a greater incidence of gastrointestinal grade 3 or 4 adverse events (see PRECAUTIONS: *Geriatric Use*). Among the 14 patients 80 years of age and greater treated with capecitabine, three (21.4%), three (21.4%) and one (7.1%) patients experienced reversible grade 3 or 4 diarrhea, nausea and vomiting, respectively.

Among the 313 patients age 60 to 79 years old, the incidence of gastrointestinal toxicity was similar to that in the overall population.

Pregnancy: XELODA may cause fetal harm when given to a pregnant woman. Capecitabine at doses of 198 mg/kg/day during organogenesis caused teratogenic 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. Teratogenic malformations in mice included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilation of cerebral ventricles. At doses of 90 mg/kg/day, capecitabine given to pregnant monkeys during organogenesis caused fetal death. This dose produced 5'-DFUR AUC values about 0.6 times the corresponding values in patients administered the recommended daily dose. There are no adequate and well-controlled studies in pregnant women using XELODA. If the drug is used during pregnancy, or if the patient becomes

pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with XELODA.

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

Hand-and-Foot Syndrome: Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) is characterized by the following: numbness, dysesthesia/paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering and severe pain. Grade 2 hand-and-foot syndrome is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 hand-and-foot syndrome is defined as moist desquamation, ulceration, blistering and 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).

Cardiac: There has been cardiotoxicity associated with fluorinated pyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiograph changes. These adverse events may be more common in patients with a prior history of coronary artery disease.

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

Hyperbilirubinemia: Grade 3 or 4 hyperbilirubinemia occurred in 17% (n=97) of 570 patients with either metastatic breast or colorectal cancer who received a dose of 2510 mg/m^2 daily for 2 weeks followed by a 1-week rest period. Of 339 patients who had hepatic metastases at baseline and 231 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 21.2% and 10.4%, respectively. Seventy-four (76%) of the 97 patients with grade 3 or 4 hyperbilirubinemia also had concurrent elevations in alkaline phosphatase and/or hepatic transaminases; 6% of these were grade 3 or 4. Only 4 patients (4%) had elevated hepatic transaminases without a concurrent elevation in alkaline phosphatase. If drug related grade 2-4 elevations in bilirubin occur, administration of XELODA should be immediately interrupted until the hyperbilirubinemia resolves or decreases in intensity to grade 1. NCIC grade 2 hyperbilirubinemia is defined as 1.5 x normal, grade 3 hyperbilirubinemia as 1.5-3 x normal and grade 4 hyperbilirubinemia as >3 x normal. (See recommended dose modifications under DOSAGE AND ADMINISTRATION.)

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Hematologic: In 570 patients with either metastatic breast or colorectal cancer who received a dose of 2510 mg/m^2 administered daily for 2 weeks followed by a 1-week rest period, 4%, 2%, and 3% of patients had grade 3 or 4 neutropenia, thrombocytopenia and decreases in hemoglobin, respectively.

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

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

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

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

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

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.

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

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

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

Drug-Drug Interactions:

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

Coumarin Anticoagulants: Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Patients taking coumarin-derivative anticoagulants concomitantly with capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR) (see WARNINGS: *Coagulopathy*).

Phenytoin: Postmarketing reports indicate that some patients receiving capecitabine and phenytoin had toxicity associated with elevated phenytoin levels. The level of phenytoin should be carefully monitored in patients taking XELODA and phenytoin dose may need to be reduced (see DOSAGE AND ADMINISTRATION: *Dose Modification Guidelines*).

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

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

Nursing Women: It is not known whether the 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, it is recommended that nursing be discontinued when receiving XELODA therapy.

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

Geriatric Use: No separate studies have been conducted to examine the effect of age on the pharmacokinetics of capecitabine and its metabolites. Patients ≥80 years old may experience a greater incidence of gastrointestinal grade 3 or 4 adverse events (see WARNINGS). Among the 14 patients 80 years of age and greater treated with capecitabine, 21.4%, 21.4% and 7.1% experienced grade 3 or 4 diarrhea, nausea and vomiting, respectively. Among the 313 patients 60 to 79 years old, the incidence was similar to the overall population.

The elderly may be pharmacodynamically more sensitive to the toxic effects of 5-FU. Physicians should pay particular attention to monitoring the adverse effects of XELODA in the elderly.

ADVERSE REACTIONS:

The following table shows the adverse events occurring in ≥5% of patients reported as at least remotely related to the administration of XELODA. Rates are rounded to the nearest whole number. The data are shown both for the study in stage IV breast cancer and for a group of 570 patients with breast and colorectal cancer who received a dose of 2510 mg/m^2 administered daily for 2 weeks followed by a 1-week rest period. The 570 patients were enrolled in 6 clinical trials (162 from the breast cancer trial described under CLINICAL STUDIES, 83 other patients with breast cancer and 325 patients with colorectal cancer). The mean duration of treatment was 121 days. A total of 71 patients (13%) discontinued treatment because of adverse events/intercurrent illness.

Table 3. Percent Incidence of Adverse Events Considered Remotely, Possibly or Probably Related to Treatment in ≥5% of Patients

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)			Overall Safety Database (n=570)		
Body System/Adverse Event	**Total**	**Grade 3**	**Grade 4**	**Total**	**Grade 3**	**Grade 4**
GI						
Diarrhea	57	12	3	50	11	2
Nausea	53	4	–	44	4	–
Vomiting	37	4	–	26	3	–
Stomatitis	24	7	–	23	4	–
Abdominal pain	20	4	–	17	4	–
Constipation	15	1	–	9	1	–
Dyspepsia	8	–	–	6	–	–
Skin and Subcutaneous						
Hand-and-Foot Syndrome	57	11	–	45	13	–
Dermatitis	37	1	–	31	1	–
Nail disorder	7	–	–	4	–	–

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Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)			Overall Safety Database (n=570)		
Body System/Adverse Event	**Total**	**Grade 3**	**Grade 4**	**Total**	**Grade 3**	**Grade 4**
General						
Fatigue	41	8	–	34	5	–
Pyrexia	12	1	–	10	–	–
Pain in limb	6	1	–	4	–	–
Neurological						
Paraesthesia	21	1	–	12	–	–
Headache	9	1	–	7	1	–
Dizziness	8	–	–	5	–	–
Insomnia	8	–	–	3	–	–
Metabolism						
Anorexia	23	3	–	20	2	–
Dehydration	7	4	1	5	2	1
Eye						
Eye irritation	15	–	–	10	–	–
Musculoskeletal						
Myalgia	9	–	–	4	–	–
Cardiac						
Edema	9	1	–	6	–	–
Blood						
Neutropenia	26	2	2	22	3	2
Thrombocytopenia	24	3	1	21	1	1
Anemia	72	3	1	74	2	1
Lymphopenia	94	44	15	94	36	10
Hepatobiliary						
Hyperbilirubinemia	22	9	2	34	14	3

– Not observed or applicable.

Shown below by body system are the adverse events in <5% of patients reported as related to the administration of XELODA and that were clinically at least remotely relevant. In parentheses is the incidence of grade 3 or 4 occurrences of each adverse event.

Gastrointestinal: intestinal obstruction (1.1), rectal bleeding (0.4), GI hemorrhage (0.2), esophagitis (0.4), gastritis, colitis, duodenitis, haematemesis, necrotizing enterocolitis

Skin: increased sweating (0.2), photosensitivity (0.2), radiation recall syndrome (0.2)

General: chest pain (0.2)

Neurological: ataxia (0.4), encephalopathy (0.2), depressed level of consciousness (0.2), loss of consciousness (0.2)

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Metabolism: cachexia (0.4), hypertriglyceridemia (0.2)

Respiratory: dyspnea (0.5), epistaxis (0.2), bronchospasm (0.2), respiratory distress (0.2)

Infections: oral candidiasis (0.2), upper respiratory tract infection (0.2), urinary tract infection (0.2), bronchitis (0.2), pneumonia (0.2), sepsis (0.4), bronchopneumonia (0.2), gastroenteritis (0.2), gastrointestinal candidiasis (0.2), laryngitis (0.2), esophageal candidiasis (0.2)

Musculoskeletal: bone pain (0.2), joint stiffness (0.2)

Cardiac: angina pectoris (0.2), cardiomyopathy

Vascular: hypotension (0.2), hypertension (0.2), venous phlebitis and thrombophlebitis (0.2), deep venous thrombosis (0.7), lymphoedema (0.2), pulmonary embolism (0.4), cerebrovascular accident (0.2)

Blood: coagulation disorder (0.2), idiopathic thrombocytopenic purpura (0.2), pancytopenia (0.2)

Psychiatric: confusion (0.2)

Renal and Urinary: nocturia (0.2)

Hepatobiliary: hepatic fibrosis (0.2), cholestatic hepatitis (0.2), hepatitis (0.2)

Immune System: drug hypersensitivity (0.2)

OVERDOSAGE: *Acute:* Based on experience in animals and in humans treated up to doses of 3514 mg/m^2/day, the anticipated manifestations of acute overdose would be 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 has been reported, dialysis may be of benefit in reducing circulating concentrations of 5'-DFUR, a low-molecular weight metabolite of the parent compound.

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

DOSAGE AND ADMINISTRATION: The recommended dose of XELODA is 2500 mg/m^2 administered orally daily with food for 2 weeks followed by a 1-week rest period given as 3 week cycles. The XELODA daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. XELODA tablets should be swallowed with water. The following table displays the total daily dose by body surface area and the number of tablets to be taken at each dose.

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Table 4. XELODA Dose Calculation According to Body Surface Area

Dose level 2500 mg/m^2/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**
≤ 1.24	3000	0	3
1.25 - 1.36	3300	1	3
1.37 - 1.51	3600	2	3
1.52 - 1.64	4000	0	4
1.65 - 1.76	4300	1	4
1.77 - 1.91	4600	2	4
1.92 - 2.04	5000	0	5
2.05 - 2.17	5300	1	5
≥ 2.18	5600	2	5

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

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

The phenytoin dose may need to be reduced when phenytoin is concomitantly administered with XELODA (see PRECAUTIONS: *Drug-Drug Interactions*).

Table 5. Recommended Dose Modifications

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

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Toxicity NCIC Grades*	During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
• *Grade 4*		
-1st appearance	Discontinue permanently *or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%

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

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

Adjustment of Starting Dose in Special Populations:

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

Renal Impairment: In patients with moderate renal impairment (creatinine clearance 30-50 mL/min [Cockroft and Gault, as shown below]) at baseline, a dose reduction to 75% of the XELODA starting dose (from 2500 mg/m^2/day to 1900 mg/m^2/day) is recommended. In patients with mild renal impairment (creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event with subsequent dose adjustments as outlined in the table above. XELODA is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).

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

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Geriatrics: The elderly may be pharmacodynamically more sensitive to the toxic effects of 5-FU and therefore, physicians should exercise caution in monitoring the effects of XELODA in the elderly. Insufficient data are available to provide a dosage recommendation.

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

150 mg

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

500 mg

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

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

*Maalox is a registered trademark of Novartis.

R_X only

Roche Pharmaceuticals

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Revised: November 2000
Printed in USA

XELODA® (capecitabine)

PATIENT PACKAGE INSERT (text only):

Patient Information About XELODA® (capecitabine) Tablets

This information will help you learn more about XELODA® (capecitabine) Tablets. It cannot, however, cover all possible precautions or side effects associated with XELODA nor does it list all the benefits and risks of XELODA. Your doctor should always be your first choice for detailed information about your medical condition and your treatment. Be sure to ask your doctor about any questions you may have.

What is XELODA?

- XELODA [zeh-LOE-duh] is an oral medication for the treatment of advanced breast cancer resistant to treatment with paclitaxel [pak-lih-TAK-sil] and an anthracycline [ann-thruh-SYE-kleen]-containing chemotherapy regimen. Paclitaxel is also known as Taxol®*. Anthracyclines include Adriamycin®† or doxorubicin.

- XELODA tablets come in two strengths: 150 mg (light peach) and 500 mg (peach).

How does XELODA work?

XELODA is converted in the body to the substance 5-fluorouracil. In some patients, this substance kills cancer cells and decreases the size of the tumor.

Who should not take XELODA?

- Patients allergic to 5-fluorouracil.

- Studies in animals suggest that XELODA may cause serious harm to an unborn child. No studies have been done with pregnant women. If you are pregnant, be sure to discuss with your doctor whether XELODA is right for you. Also, tell your doctor if you are nursing.

- Patients with severe renal impairment. Please inform your doctor if you know of any renal impairment that you may have. Your doctor may either prescribe a different drug or reduce the XELODA dose.

How should I take XELODA?

Your doctor will prescribe a dose and treatment regimen that is right for *you*. Your doctor may want you to take a combination of *150 mg* and *500 mg* tablets for each dose. If a combination of tablets is prescribed, it is very important that you correctly identify the tablets. Taking the wrong tablets could result in an overdose (too much medication) or underdose (too little medication). The 150 mg tablets are light peach in color and have 150 engraved on one side. The 500 mg tablets are peach in color and have 500 engraved on one side.

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- Take the tablets in the combination prescribed by your doctor for your **morning and evening** doses.
- Take the tablets within **30 minutes after the end of a meal** (breakfast and dinner).
- XELODA tablets should be **swallowed with water.**
- It is important that you take all your medication as prescribed by your doctor.
- If you are taking the vitamin folic acid, please inform your doctor.
- If you are taking phenytoin (also known as Dilantin®‡), please inform your doctor. Your doctor may need to more frequently test the levels of phenytoin in your blood and/or change the dose of phenytoin that you are taking.
- If you are taking warfarin (also known as Coumadin®§), please inform your doctor. Your doctor may need to more frequently check how quickly your blood is clotting.

How long will I have to take XELODA?

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

What if I miss a dose?

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

What are the most common side effects of XELODA?

The most common side effects of XELODA are:

- diarrhea, nausea, vomiting, stomatitis (sores in mouth and throat), abdominal pain, constipation, loss of appetite or decreased appetite, and dehydration (excessive water loss from the body).
- hand-and-foot syndrome (palms of the hands or soles of the feet tingle, become numb, painful, swollen or red), rash, dry or itchy skin.
- tiredness, weakness, dizziness, headache, and fever.

When should I call my doctor?

It is important that you **CONTACT YOUR DOCTOR IMMEDIATELY** if you experience the following side effects. This will help reduce the likelihood that the side effect will continue or

become serious. Your doctor may instruct you to decrease the dose and/or temporarily discontinue treatment with XELODA.

STOP taking XELODA immediately and contact your doctor if any of these symptoms occur:

- ***Diarrhea:*** if you have more than 4 bowel movements each day or any diarrhea at night.
- ***Vomiting:*** if you vomit more than once in a 24-hour time period.
- ***Nausea:*** if you lose your appetite, and the amount of food you eat each day is much less than usual.
- ***Stomatitis:*** if you have pain, redness, swelling, or sores in your mouth.
- ***Hand-and-foot syndrome:*** if you have pain, swelling or redness of hands and/or feet.
- ***Fever or Infection:*** if you have a temperature of 100.5°F or greater, or other evidence of infection.

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

How should I store and use XELODA?

- Never share XELODA with anyone.
- XELODA should be stored at normal room temperature (about 65° to 85°F).
- Keep this and all other medications out of the reach of children.
- In case of accidental ingestion or if you suspect that more than the prescribed dose of this medication has been taken, contact your doctor or local poison control center or emergency room IMMEDIATELY.
- Medicines are sometimes prescribed for uses other than those listed in this leaflet. If you have any questions or concerns, or want more information about XELODA, contact your doctor or pharmacist.

* Taxol is a registered trademark of Bristol-Myers Squibb Company.
† Adriamycin is a registered trademark of Pharmacia & Upjohn Company.
‡ Dilantin is a registered trademark of Parke-Davis.
§ Coumadin is a registered trademark of DuPont Pharma.