

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

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

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

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

Drug-Drug Interactions

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

Anticoagulants: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly (see **Boxed WARNING** and **CLINICAL PHARMACOLOGY**). Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating XELODA therapy and, in a few cases, within 1 month after stopping XELODA. These events occurred in patients with and without liver metastases. In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites (see **CLINICAL PHARMACOLOGY**).

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

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

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

Pregnancy

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

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

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

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

ADVERSE REACTIONS

Adjuvant Colon Cancer: Table 1 shows the adverse events 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/m² twice a day of XELODA administered for 2 weeks followed by a 1-week rest period, and 974 patients were administered 5-FU and leucovorin (20 mg/m² leucovorin IV followed by 425 mg/m² 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 events. 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 2 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 1 Percent Incidence of Adverse Events Reported in ≥5% of Patients Treated With XELODA or 5-FU/LV for Colon Cancer in the Adjuvant Setting (Safety Population)

Body System/ Adverse Event	Adjuvant Treatment for Colon Cancer (N=1969)			
	XELODA (N=995)		5-FU/LV (N=974)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
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
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 2 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)	IV 5-FU/LV (n=974)
	Grade 3/4 (%)	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 x upper limit of normal (ULN) range, and grade 4 a value of > 3.0 x ULN. The NCIC CTC Version 2 and above define a grade 3 bilirubin value of >3.0 to 10.0 x ULN, and grade 4 values >10.0 x ULN.

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/m² basis).

Maalox is a registered trademark of Novartis Consumer Health. Taxotere is a registered trademark of Aventis Pharmaceuticals Inc.

Rx only



Pharmaceuticals

Roche Laboratories Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
www.rocheusa.com

Revised: June 2005

Copyright ©1999-2005 by Roche Laboratories Inc. All rights reserved.