XELODA®
(capecitabine)
TABLETS

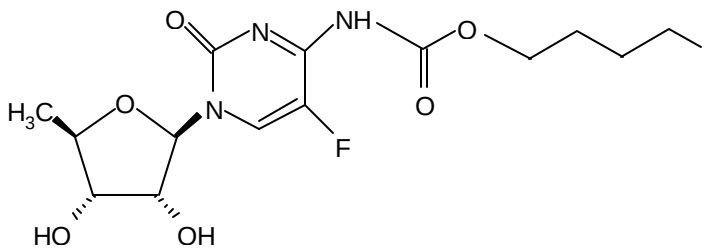
WARNING

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

DESCRIPTION

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

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



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

XELODA® (capecitabine)

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

Special Populations:

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

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

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

Drug-Drug Interactions:

Anticoagulants: In four patients with cancer, chronic administration of capecitabine (1250 mg/m^2 bid) with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8 fold, and the maximum observed mean INR value was increased by 91% (see Boxed WARNING and PRECAUTIONS: *Drug-Drug Interactions*).

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

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

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

Drug-Drug Interactions:

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

Anticoagulants: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly (see Boxed WARNING and CLINICAL PHARMACOLOGY). Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating XELODA therapy and, in a few cases, within one 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 Modification Guidelines*). Postmarketing reports indicate that some patients receiving XELODA and phenytoin had toxicity associated with elevated phenytoin levels. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine and/or its metabolites (see PRECAUTIONS: *Drug-Drug Interactions: Anticoagulants*).