PRODUCT MONOGRAPH

# PrXELODA®

capecitabine tablets

Tablets 150 mg and 500 mg

Manufacturer's Standard

Antineoplastic Agent

Hoffmann-La Roche Limited
7070 Mississauga Road
Mississauga, Ontario
L5N 5M8

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www.rochecanada.com

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**PrXELODA®**
capecitabine tablets

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength | Non-medicinal Ingredients |
|---|---|---|
| Oral | Tablets 150 mg and 500 mg | Non-medicinal ingredients (alphabetical order): croscarmellose sodium, hydroxypropyl methylcellulose, iron oxides (yellow and red), lactose anhydrous, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide. |

### INDICATIONS AND CLINICAL USE

**Caution: XELODA (capecitabine) is a potent drug and should be prescribed only by physicians experienced with cancer chemotherapeutic drugs.**

XELODA (capecitabine) is indicated for:

**Colorectal Cancer**
**Monotherapy**

- XELODA (capecitabine) is indicated for the adjuvant treatment of patients with stage III (Dukes' stage C) colon cancer.
- XELODA is also indicated for the first-line treatment of patients with metastatic colorectal cancer.

**Combination Therapy**
XELODA in combination with oxaliplatin is indicated for the treatment of metastatic colorectal cancer following failure of irinotecan-containing combination chemotherapy.

In second-line metastatic disease, subgroup analyses for PFS and OS for age suggest that XELODA in combination with oxaliplatin may be less effective in patients over the age of 65. Clinical studies suggest an increase in the incidence of adverse events. See CLINICAL TRIALS and WARNINGS AND PRECAUTIONS.

**Breast Cancer**
**Monotherapy**

XELODA is also indicated for the treatment of advanced or metastatic breast cancer after failure of standard therapy including a taxane, unless therapy with a taxane is clinically contraindicated.

**Combination Therapy**
XELODA in combination with docetaxel is indicated for the treatment of patients with advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy.

**Pediatrics (< 18 years of age):**
The safety and effectiveness of XELODA in persons <18 years of age has not been established.

## CONTRAINDICATIONS

- Patients who are hypersensitive to capecitabine, or to 5-fluorouracil or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Severe renal impairment (calculated creatinine clearance below 30 mL/min, or 0.5 mL/s)Contraindicated in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. Testing for DPD deficiency should be considered prior to treatment, based on the local availability and current guidelines (see WARNINGS and PRECAUTIONS/'Dihydropyrimidine dehydrogenase (DPD) deficiency' and 'Monitoring and Laboratory Tests').
- Due to potentially fatal drug interaction, XELODA should not be administered concomitantly with sorivudine[1] or its chemically related analogues, such as brivudine.

If contraindications exist to any of the agents in a combination regimen, that agent should not be used.

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- Acute renal failure secondary to dehydration can be fatal. If Grade 2 (or higher) dehydration occurs, XELODA treatment should be immediately interrupted and the dehydration corrected (see Endocrine and Metabolism - Dehydration below).
- Similar to that of other fluorinated pyrimidines sudden death due to cardiotoxicity has been observed with XELODA (see Cardiovascular below).
- XELODA can induce severe skin reactions such as hand-and-foot syndrome, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. If grade 2 (or higher) event occurs, administration of XELODA should be immediately interrupted (see Immune and Skin below).
- Severe toxicity (e.g. stomatitis, diarrhea, mucosal inflammation, neutropenia and

[1] sorivudine and its chemically related analogues, such as brivudine are not authorized for sale in Canada.

neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity, an enzyme involved in fluorouracil degradation. Fatalities have been reported. Testing for DPD deficiency should be considered prior to treatment, based on the local availability and current guidelines. (see Endocrine and Metabolism- DPD deficiency below).

- Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA concomitantly with coumarin-derived anticoagulants such as warfarin. Patients taking coumarin-derivative anticoagulants concomitantly with XELODA should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly (see Hematologic below).

**General**

**If toxicity on therapy occurs, XELODA should be interrupted until the event resolves, or the severity decreases when the following toxicities occur at a severity of grade 2 or greater: diarrhea, hand-foot syndrome, nausea, hyperbilirubinemia, vomiting or stomatitis (see DOSAGE AND ADMINISTRATION).**

Patients and patients' caregivers should be informed of the expected adverse effects of XELODA, particularly of diarrhea, nausea, vomiting, and hand-and-foot syndrome and stomatitis. The frequent oral administration of XELODA allows patient specific dose adaptations during therapy (see DOSAGE AND ADMINISTRATION). Most adverse reactions are reversible and do not require discontinuation, although doses may need to be withheld or reduced (see DOSAGE AND ADMINISTRATION). Patients should be taught to recognize and report the common grade 2 toxicities associated with XELODA treatment (please refer to CONSUMER INFORMATION).

If XELODA is prescribed in combination with docetaxel, patients and patients' caregivers should be informed of the expected adverse effects of the combination of XELODA and docetaxel (see Table 11).

***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 agents (e.g. loperamide) should be prescribed for symptom control (see DOSAGE AND ADMINISTRATION).

***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. Standard anti-nausea agents should be prescribed for symptom control (see DOSAGE AND ADMINISTRATION).

***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. Standard anti-emetic agents should be prescribed for symptom control (see DOSAGE AND ADMINISTRATION).

***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 or greater (painful erythema, edema or ulcers, but are able to eat) should be instructed to stop taking XELODA immediately. Symptomatic treatment should be prescribed (see DOSAGE AND ADMINISTRATION).

**Effect on Ability to Drive and Use Machines**

XELODA has moderate influence on the ability to drive and use machines. Patients should be advised to use caution when driving or using machines if they experience ADRs such as dizziness, fatigue, and or nausea during treatment with XELODA.

**Carcinogenesis and Mutagenesis**

Although there was no evidence for oncogenic potential of capecitabine in a two-year carcinogenicity study in mice, capecitabine was clastogenic *in vitro* in human lymphocytes (similar to other nucleoside analogues such as 5-FU). There was also a positive trend in the *in vivo* mouse micronucleus assay (see TOXICOLOGY-Carcinogenicity, Mutagenicity, and Genotoxicity studies).

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with XELODA (see Special Populations below) and be provided with appropriate counselling if not currently using contraceptives. Males are advised not to father a child during treatment.

**Cardiovascular**

The spectrum of cardiotoxicity observed with XELODA is similar to that of other fluorinated pyrimidines. This includes myocardial infarction, angina, dysrhythmias, cardiac arrest, sudden death, cardiomyopathy, cardiac failure, and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease. A thorough QT interval prolongation assessment study of XELODA has not been conducted.

**Endocrine and Metabolism**

**Dehydration**

Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated. If Grade 2 (or higher) dehydration occurs, XELODA treatment should be immediately interrupted and the dehydration corrected.[2] Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be applied for the precipitating adverse event as necessary (see DOSAGE AND ADMINISTRATION section).

Dehydration may cause acute renal failure, especially in patients with pre-existing compromised

[2] NCIC grade 2 dehydration is defined as IV fluids indicated <24 hours, grade 3 dehydration is defined as IV fluids indicated ≥24 hours, grade 4 dehydration is defined as life-threatening consequences (e.g. hemodynamic collapse), and grade 5 dehydration as death.

renal function or when capecitabine is given concomitantly with known nephrotoxic agents. Fatal outcome of renal failure has been reported in these situations (see ADVERSE REACTIONS).

**Dihydropyrimidine dehydrogenase (DPD) deficiency**
Patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus that cause complete or near complete absence of DPD activity, are at the highest risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil. These patients should not be treated with XELODA. No dose has been proven safe for patients with complete absence of DPD activity (see CONTRAINDICATIONS).

Patients with certain heterozygous DPYD variants (eg. DPYD*2A variant) that may cause partial DPD deficiency have been shown to have increased risk of severe toxicity when treated with capecitabine. For patients with partial DPD deficiency where the benefits of XELODA are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution, initially with a substantial dose reduction and frequent subsequent monitoring and dose adjustment according to toxicity.

Testing for DPD deficiency should be considered prior to treatment, based on the local availability and current guidelines.

In patients with unrecognised DPD deficiency treated with capecitabine as well as patients who test negative for specific DPYD variations, life-threatening toxicities manifesting as acute overdose may occur. In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities (see DOSAGE AND ADMINISTRATION).

**Gastrointestinal**
**Diarrhea**
XELODA very frequently induces diarrhea, which can sometimes be severe. Patients with severe diarrhea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement (see Monitoring and Laboratory tests). If grade 2 (or higher) diarrhea occurs, administration of XELODA should be immediately interrupted until diarrhea resolves or decreases in intensity to grade 1[3]. Standard antidiarrheal agents (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Dose reduction should be applied as necessary (see DOSAGE AND ADMINISTRATION section). Necrotizing enterocolitis (typhlitis) has been reported.

[3] National Cancer Institute of Canada (NCIC) grade 1 diarrhea is defined as an increase of < 4 stools per day over baseline, mild increase in ostomy output compared to baseline, 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, grade 4 diarrhea as an increase of 10 stools/day or grossly bloody diarrhea or the need for parenteral support, and grade 5 diarrhea as death.

**Hematologic**

In 251 patients with metastatic breast cancer who received 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.

In 875 patients with either metastatic breast or colorectal cancer who received XELODA monotherapy, 3.2%, 1.7%, and 2.4% of patients had grade 3/4 neutropenia, thrombocytopenia and decreases in hemoglobin, respectively.

**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 (see DOSAGE AND ADMINISTRATION - Haematology).**

Altered coagulation parameters and/or bleeding have been reported in patients taking XELODA concomitantly with coumarin-derived anticoagulants such as warfarin. 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 (see Monitoring and Laboratory Tests and DRUG INTERACTIONS: *Coumarin Anticoagulants*).

**Hepatic/Biliary**

**Hepatic Insufficiency**

Patients with hepatic impairment should be carefully monitored when XELODA is administered (see Monitoring and Laboratory Tests). However, the effect of hepatic impairment not due to liver metastases or of severe hepatic impairment on the disposition of XELODA is not known.

**Hyperbilirubinemia**

In 251 patients with metastatic breast cancer who received a combination of XELODA and docetaxel, grade 3 and 4 hyperbilirubinemia occurred in 6.8% (n=17) and 2% (n=5), respectively.

In 875 patients with either metastatic breast or colorectal cancer treated with XELODA monotherapy, grade 3 hyperbilirubinemia occurred in 133 (15.2%) and grade 4 hyperbilirubinemia occurred in 34 (3.9%) patients with either metastatic breast or colorectal cancer. If drug related grade 2, 3 or 4† elevations in bilirubin occur, administration of XELODA should be immediately interrupted until the hyperbilirubinemia resolves or decreases in intensity to grade 1. Following grade 3 or 4 hyperbilirubinemia, subsequent doses of XELODA should be decreased (see DOSAGE AND ADMINISTRATION).

**Immune**

XELODA can induce severe skin reactions such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (see ADVERSE REACTIONS). XELODA should be permanently discontinued in patients who experience a severe skin reaction possibly attributable to XELODA treatment.

Rarely, unexpected and potentially fatal severe toxicities including neutropenia leading to local and fatal systemic infections following exposure to XELODA have been observed.

**Neurologic**

Very rare adverse drug reaction leukoencephalopathy has been identified during post-marketing exposure.

**Renal**

**Renal Insufficiency**

In patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min [Cockroft and Gault])* at baseline, a dose reduction to 75% of the XELODA starting dose when used as monotherapy or in combination with docetaxel is recommended based upon pharmacokinetic and safety data. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event, with subsequent dose adjustment as outlined in Table 18 in the DOSAGE AND ADMINISTRATION section.

Physicians should exercise caution when XELODA is administered to patients with impaired renal function. As seen with 5-FU, the incidence of treatment-related grade 3 or 4 adverse events was higher in patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min).

**Skin**

**Hand-and-Foot Syndrome**

Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) can occur in patients receiving XELODA either as monotherapy or in combination therapy. Persistent or severe hand-foot syndrome (grade 2 and above) can eventually lead to loss of fingerprints, which could impact patient identification. For patients receiving XELODA monotherapy in the metastatic setting, median time to onset was 79 days (range from 11 to 360 days) with a severity range of grades 1 to 3*. 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). For XELODA in combination with docetaxel, hand-and-foot syndrome was more common in patients in the combination therapy arm than in the monotherapy arm (63% vs. 8%).

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* Cockroft-Gault Formula for males: $\text{Creatinine clearance (mL/min)} = \frac{(140\text{-age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$

Cockroft-Gault Formula for females: Creatinine clearance (mL/min)= 0.85 x male value

Creatinine clearance in SI units (mL/s) = 0.01667 x value obtained from above formula in mL/min

* Grade 1 hand-and-foot syndrome is defined by numbness, dysesthesia/paresthesia, tingling, 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 that results in discomfort affecting the patient's activities of daily living and grade 3 hand-and-foot syndrome is defined as moist desquamation, ulceration, blistering or severe pain of the hands and/or feet that results in severe discomfort that causes the patient to be unable to work or perform activities of daily living.

**Special Populations**

**Females and Males of Reproductive Potential:**

**Fertility:**
Based on evidence from animal studies, Xeloda may impair fertility in females and males of reproductive potential (see TOXICOLOGY).

**Females:**
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with XELODA and be provided with appropriate counselling if not currently using contraceptives. An effective method of contraception should be used during treatment and for 6 months after the last dose of XELODA. If the patient becomes pregnant while receiving XELODA, the potential hazard to the fetus must be explained. Pregnancy testing is recommended for females of reproductive potential prior initiating XELODA. (See Monitoring and Laboratory tests)

**Males:**
Based on genetic toxicity findings, male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of XELODA.

**Pregnant Women:** 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 (see Carcinogenesis and Mutagenesis above). XELODA was found to be teratogenic and embryolethal in mice and embryolethal in monkeys (see TOXICOLOGY).

**Lactation:** No studies have been conducted to assess the impact of XELODA on milk production or its presence in human breast milk. In a study of single oral administration of capecitabine in lactating mice, it was found that a significant amount of the capecitabine metabolites is transferred to the milk. Because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving XELODA therapy and for 2 weeks after the final dose.

**Pediatrics: (<18 years of age)**: The safety and effectiveness of XELODA in persons <18 years of age has not been established.

**Geriatrics**:
***XELODA in Combination with Docetaxel:*** An analysis of safety data in patients equal to or greater than 60 years of age showed an increase in the incidence of treatment-related Grade 3 and 4 adverse events, treatment-related serious adverse events and early withdrawals from treatment due to adverse events compared to patients less than 60 years of age. The incidence of grade 3 or

4 stomatitis was greater in the 60 to 70 year old patient group (30%) than the general population (13%) (see DOSAGE AND ADMINISTRATION).

***XELODA in Combination with Oxaliplatin:*** In the second-line setting, subgroup analyses for PFS (EP population) and OS (ITT population) for age suggest that XELOX may be less effective than FOLFOX-4 in patients ≥ 65 years of age (HR 1.32, 95% CI, 0.98-1.78 and HR 1.34, 95% CI, 1.00-1.80, respectively). Physicians are advised to assess risks and benefits in these patients.

In the second-line setting, an analysis of safety data in patients equal to or greater than 65 years of age showed an increase in the incidence of treatment related serious adverse events, treatment related Grade 3 and 4 adverse events, gastrointestinal grade 3/4 events (particularly diarrhea), and patients who discontinued trial treatment. In addition, deaths up to 60 days after treatment start and deaths up to 28 days after last dose were slightly higher in older patients (see Monitoring and Laboratory Tests).

***XELODA Monotherapy:*** Patients ≥80 years old may experience a greater incidence of gastrointestinal grade 3/4 events (see DOSAGE AND ADMINISTRATION).

**Monitoring and Laboratory Tests**

- Testing for DPD deficiency should be considered prior to treatment, based on the local availability and current guidelines. (See WARNINGS AND PRECAUTIONS/DPD deficiency)
- Patients taking coumarin-derivative anticoagulants concomitantly with XELODA should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly (see DRUG INTERACTIONS: Coumarin Anticoagulants).
- Careful monitoring of patients ≥60 years of age is advisable (see WARNINGS AND PRECAUTIONS: Geriatrics).
- Patients with severe diarrhea should be monitored for symptoms of dehydration (see WARNINGS AND PRECAUTIONS: Gastrointestinal and Endocrine and Metabolism)
- Patients with hepatic impairment or renal insufficiency should be carefully monitored when XELODA is administered (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION: Hepatic Impairment)
- Patients should be carefully monitored for toxicity (see DOSAGE AND ADMINISTRATION- Dose Modification Guidelines).
- Pregnancy testing is recommended for females of reproductive potential prior initiating XELODA. (See WARNINGS AND PRECAUTIONS/Special Populations)
- Patients taking phenytoin concomitantly with XELODA should be regularly monitored for increased phenytoin plasma concentrations. (See Drug Interactions)

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

1.1.1.1 Adverse drug reactions (ADRs) considered by the investigator to be possibly, probably, or remotely related to the administration of XELODA have been obtained from clinical studies conducted with XELODA monotherapy (in adjuvant therapy of colon cancer, in metastatic colorectal cancer and metastatic breast cancer), and clinical studies conducted with XELODA in combination with docetaxel (metastatic breast cancer) or in combination with oxaliplatin (metastatic colorectal cancer).

### Clinical Trial Adverse Drug Reactions

#### Colorectal Cancer, Monotherapy

***Adjuvant Colon Cancer***

Safety data of XELODA monotherapy were reported from one phase III trial in adjuvant colon cancer (995 patients treated with XELODA and 974 treated with i.v. 5FU/LV). The most frequently reported treatment related adverse events (≥ 10%) for XELODA in this trial were gastrointestinal disorders, especially diarrhea, stomatitis, nausea, vomiting, hand-foot syndrome, fatigue and lethargy. The most frequent treatment-related undesirable effects (≥ 5%) reported in this trial are presented in the following table (Table 1).

**Table 1 Summary of ADRs Reported in ≥ 5% of Patients with Colon Cancer Treated with XELODA Monotherapy or i.v. 5-FU/LV in the Adjuvant Setting**

| **Adverse Event** | **XELODA 1250 mg/m$^2$/bid (n=995)** | | **i.v. 5-FU/LV* (n= 974)** | |
|---|---|---|---|---|
| **Body System/Adverse Event** | **Total %** | **Grade 3/4 %** | **Total %** | **Grade 3/4 %** |
| **Gastrointestinal** | | | | |
| Diarrhea | 46 | 11 | 64 | 13 |
| Stomatitis | 22 | 2 | 60 | 14 |
| Nausea | 33 | 2 | 47 | 2 |
| Vomiting | 14 | 2 | 20 | 1 |
| Abdominal pain | 10 | 2 | 13 | 1 |
| Constipation | 6 | - | 7 | <1 |
| Abdominal pain upper | 6 | <1 | 5 | <1 |
| Dyspepsia | 5 | <1 | 4 | - |
| **Skin and Subcutaneous** | | | | |
| Hand-foot Syndrome** | 60 | 17 | 9 | <1 |
| Alopecia | 6 | - | 22 | <1 |
| Rash | 6 | - | 8 | - |
| Erythema | 6 | 1 | 5 | <1 |

| Adverse Event | XELODA 1250 mg/m$^2$/bid (n=995) | | i.v. 5-FU/LV* (n= 974) | |
|---|---|---|---|---|
| **Body System/Adverse Event** | **Total %** | **Grade 3/4 %** | **Total %** | **Grade 3/4 %** |
| **General Disorders** | | | | |
| Fatigue | 15 | <1 | 15 | 1 |
| Lethargy | 10 | <1 | 9 | <1 |
| Asthenia | 9 | <1 | 9 | 1 |
| Pyrexia | 4 | <1 | 6 | <1 |
| **Nervous System Disorders** | | | | |
| Dysgeusia | 6 | - | 9 | - |
| Dizziness | 5 | <1 | 4 | - |
| **Metabolism and Nutrition Disorders** Anorexia | 9 | <1 | 10 | <1 |
| **Eye** | | | | |
| Conjunctivitis | 5 | <1 | 5 | <1 |
| **Blood and Lymphatic System** | | | | |
| Neutropenia | 2 | <1 | 8 | 5 |

*Mayo Clinic regimen

** Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome (grade 2 and above) can eventually lead to loss of fingerprints (see WARNINGS AND PRECAUTIONS).

The following table (Table 2) displays laboratory abnormalities observed in 995 patients, regardless of relationship to treatment, with XELODA in the adjuvant treatment of colon cancer.

**Table 2 Laboratory Abnormalities[a]: XELODA Monotherapy in Adjuvant Colon Cancer**

| Parameter | XELODA 1250 mg/m$^2$ twice daily intermittent N=995 | | | |
|---|---|---|---|---|
| | **Patients with Grade 3/4 abnormality (%)** | **Patients with worsening from baseline of any grade (%)** | **Patients with worsening from baseline by 1 or 2 grades (%)** | **Patients with worsening from baseline by 3 or 4 grades (%)** |
| Increased ALAT (SGPT) | 1.6 | 27.2 | 25.9 | 1.3 |
| Increased ASAT (SGOT) | 0.7 | 28.7 | 28 | 0.7 |
| Increased alkaline phosphatase | 0.1 | 26.0 | 25.9 | 0.1 |
| Increased calcium | 1.1 | 5.2 | 4.8 | 0.4 |
| Decreased calcium | 2.3 | 13.2 | 12.4 | 0.8 |
| Decreased granulocytes | 0.3 | 2.0 | 1.7 | 0.3 |
| Decreased hemoglobin | 1.1 | 27.8 | 27.7 | 0.1 |
| Decreased lymphocytes | 13 | 51.3 | 49.2 | 2.1 |
| Decreased neutrophils | 2.2 | 30.3 | 28.4 | 1.9 |
| Decreased neutrophils/granulocytes | 2.4 | 31.0 | 28.9 | 2.1 |

| Parameter | XELODA 1250 mg/m$^2$ twice daily intermittent N=995 | | | |
|---|---|---|---|---|
| | Patients with Grade 3/4 abnormality (%) | Patients with worsening from baseline of any grade (%) | Patients with worsening from baseline by 1 or 2 grades (%) | Patients with worsening from baseline by 3 or 4 grades (%) |
| Decreased platelets | 1.0 | 17.3 | 16.8 | 0.5 |
| Decreased Potassium | 0.3 | 19.9 | 19.7 | 0.2 |
| Increased serum creatinine | 0.1 | 13.8 | 13.8 | 0 |
| Decreased Sodium | 0.4 | 17.5 | 17.1 | 0.4 |
| Increased bilirubin | 20 | 50.3 | 31.7 | 18.6 |

*The incidence of grade 3/4 white blood cell abnormalities was 1.3% in the XELODA arm and 4.9% in the I.V. 5-FU/LV arm.
[a] Laboratory abnormalities were graded according to the categories of the NCIC CTC Grading System.

## Metastatic Colorectal Cancer

Presented in the following table (Table 3) are the most frequent adverse reactions (≥5%) with intensity reported as related (remotely, possibly or probably) to the administration of XELODA (capecitabine) or 5-FU/leucovorin (LV). Rates are rounded to the nearest whole number. The data shown are from pooled phase III metastatic colorectal cancer trials, in which a total of 605 patients with metastatic colorectal cancer were treated with 2500 mg/m$^2$/day of XELODA administered for 2 weeks followed by a 1-week rest period and 604 patients were administered 5-FU and leucovorin in the Mayo regimen (20 mg/m$^2$ leucovorin I.V. followed by 425 mg/m$^2$ I.V. bolus 5-FU, on days 1 to 5, every 28 days. The adverse event profile of 5-FU/LV in this study was consistent with the published literature. 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 event/intercurrent illness.

**Table 3 Pooled Phase III Metastatic Colorectal Trials of XELODA Monotherapy vs. 5-FU/LV: Percent Incidence of Adverse Reactions in ≥5% of Patients**

| Adverse Event | XELODA (n=596) | | | 5-FU/LV (n=593) | | |
|---|---|---|---|---|---|---|
| | NCIC Grade | | | | | |
| Body System/ Adverse Event | 1 to 4 | 3 | 4 | 1 to 4 | 3 | 4 |
| **GI** | | | | | | |
| Diarrhea All | 49 | 12 | 2 | 59 | 10 | 2 |
| Nausea | 38 | 3 | - | 47 | 2 | - |
| Vomiting | 23 | 3 | - | 27 | 3 | - |
| Stomatitis All | 25 | 2 | - | 62 | 14 | 1 |
| Abdominal Pain | 17 | 4 | - | 16 | 2 | - |
| Gastrointestinal Motility Disorder | 10 | - | - | 11 | 1 | - |
| Constipation | 7 | - | - | 8 | - | - |

| Adverse Event | XELODA (n=596) | | | 5-FU/LV (n=593) | | |
|---|---|---|---|---|---|---|
| Body System/ Adverse Event | NCIC Grade | | | | | |
| | 1 to 4 | 3 | 4 | 1 to 4 | 3 | 4 |
| Oral Discomfort | 9 | - | - | 9 | - | - |
| **Skin and Subcutaneous** | | | | | | |
| Hand-and-Foot Syndrome** | 53 | 17 | - | 6 | 1 | - |
| Dermatitis | 24 | 1 | - | 23 | 1 | - |
| Skin Discoloration | 7 | - | - | 5 | - | - |
| Alopecia | 6 | - | - | 21 | - | - |
| **General** | | | | | | |
| Fatigue/Weakness | 32 | 3 | - | 38 | 3 | - |
| Pyrexia | 9 | - | - | 12 | 1 | - |
| **Neurological** | | | | | | |
| Paresthesia | 9 | - | - | 5 | - | - |
| Sensory Disturbance | 6 | - | - | 11 | - | - |
| Dizziness* | 5 | - | - | 5 | - | - |
| **Metabolism** | | | | | | |
| Appetite decreased | 20 | 1 | - | 25 | 2 | - |
| Dehydration | 4 | 2 | - | 6 | 2 | - |
| **Eye** | | | | | | |
| Eye Irritation | 11 | - | - | 8 | - | - |
| **Respiratory** | | | | | | |
| Dyspnea | 6 | - | - | 4 | - | - |
| **Cardiac** | | | | | | |
| Edema | 5 | - | - | 3 | - | - |
| **Blood and Lymphatic** | | | | | | |
| Neutropenia | 21 | 0.7 | 2 | 55 | 8 | 13 |
| Thrombocytopenia | 20 | 0.5 | 0.5 | 28 | 0.2 | 0.2 |
| Anemia | 80 | 2 | 0.2 | 82 | 1 | 0.3 |
| Lymphopenia | 93 | 29 | 8 | 92 | 30 | 8 |
| **Hepatobiliary** | | | | | | |
| Hyperbilirubinemia | 49 | 18 | 5 | 25 | 3 | 3 |

- Not observed or applicable.
* Excluding vertigo
** Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome (grade 2 and above) can eventually lead to loss of fingerprints (see WARNINGS AND PRECAUTIONS).

In the pooled phase III metastatic colorectal studies, dose reductions occurred in 34% of patients treated with capecitabine and in 42% with 5-FU. Dose reductions also occurred later with capecitabine than 5-FU/LV (median time to dose reduction was 76 and 36 days, respectively).

The hospitalization rate for the treatment-related adverse events was 11.6% for capecitabine treated patients and 18.0% for 5-FU/LV-treated patients. The predominant treatment-related adverse events leading to hospitalization in capecitabine and 5-FU/LV-treated patients, respectively, were diarrhea (4.2% vs. 3.7%), dehydration (2.2% vs. 1.5%), and stomatitis (0.2% vs. 3.7%).

**Metastatic Colorectal Cancer, Combination Therapy**

***XELODA in combination with oxaliplatin***

The following table (Table 4) shows the most frequent ADRs (≥5%) reported in patients with metastatic colorectal cancer who received second-line (Study NO16967) treatment with XELODA in combination with oxaliplatin (XELOX). The intensity of adverse events was graded according to the toxicity categories of the NCI CTCAE Grading System Version 3.0.

**Table 4 Summary of ADRs in ≥5% of Patients who Received Second-line Treatment with XELODA and Oxaliplatin for Metastatic Colorectal Cancer (Study NO16967)**

| | XELOX[a] (N=311) | | FOLFOX-4[b] (N=308) | |
|---|---|---|---|---|
| **Body system** | **All** | **Grade 3/4** | **All** | **Grade 3/4** |
| Adverse drug reaction | **%** | **%** | **%** | **%** |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 60 | 4 | 56 | 3 |
| Diarrhea | 57 | 20 | 49 | 5 |
| Vomiting | 43 | 3 | 34 | 3 |
| Stomatitis | 14 | <1 | 30 | 1 |
| Abdominal pain | 30 | 5 | 24 | 5 |
| Constipation | 16 | 2 | 26 | 3 |
| Dyspepsia | 11 | <1 | 7 | - |
| Abdominal pain upper | 6 | <1 | 6 | <1 |
| **Nervous system disorders** | | | | |
| Paraesthesia | 33 | 4 | 32 | 3 |
| Neuropathy peripheral | 13 | <1 | 10 | - |
| Peripheral sensory neuropathy | 13 | <1 | 16 | 2 |
| Dysgeusia | 7 | <1 | 11 | - |
| Neuropathy | 12 | <1 | 9 | <1 |
| Dysaesthesia | 10 | <1 | 11 | 2 |
| Dizziness | 10 | <1 | 9 | - |
| Headache | 10 | <1 | 11 | <1 |
| Lethargy | 6 | 2 | 6 | <1 |
| Hypoaesthesia | 7 | <1 | 6 | <1 |
| **General disorders and administration site conditions** | | | | |
| Fatigue | 41 | 7 | 42 | 9 |
| Asthenia | 19 | 3 | 18 | 5 |
| Oedema Peripheral | 5 | <1 | 9 | <1 |
| Pyrexia | 21 | - | 23 | <1 |
| Temperature intolerance | 5 | - | 6 | - |
| Chills | 3 | - | 6 | - |
| **Blood and lymphatic system disorders** | | | | |
| Neutropenia | 18 | 5 | 48 | 35 |
| Thrombocytopenia | 13 | 3 | 17 | 2 |
| Anaemia | 6 | 1 | 8 | 2 |
| **Metabolism and nutrition disorders** | | | | |
| Anorexia | 32 | 4 | 27 | 2 |
| Hypokalemia | 8 | 4 | 5 | 3 |
| Dehydration | 6 | 3 | 5 | 2 |

| | XELOX[a] (N=311) | | FOLFOX-4 [b] (N=308) | |
|---|---|---|---|---|
| **Body system** | **All** | **Grade 3/4** | **All** | **Grade 3/4** |
| **Skin and subcutaneous tissue disorders** | 23 | 4 | 6 | <1 |
| Palmar-plantar erythrodysaesthesia syndrome | 10 | - | 7 | <1 |
| Rash | 1 | - | 6 | - |
| Alopecia | | | | |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough | 7 | <1 | 15 | - |
| Dysaesthesia pharynx | 11 | 2 | 4 | <1 |
| Epistaxis | 3 | - | 7 | <1 |
| Dyspnea | 9 | 1 | 10 | 2 |
| Pharyngolaryngeal pain | 3 | - | 5 | - |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Pain in extremity | 6 | <1 | 5 | <1 |
| Pain in jaw | 5 | <1 | 4 | - |
| Pain in back | 10 | 2 | 14 | 3 |
| Myalgia | 4 | - | 7 | <1 |
| **Investigations** | | | | |
| Weight decreased | 6 | <1 | 6 | <1 |
| **Psychiatric disorders** | | | | |
| Insomnia | 7 | <1 | 12 | - |
| **Infections and Infestations** | | | | |
| Nasopharyngitis | 4 | - | 6 | <1 |
| **Vascular Disorders** | | | | |
| Flushing | 3 | - | 6 | - |
| **Immune System Disorders** | | | | |
| Hypersensitivity | 2 | <1 | 6 | 4 |

[a]XELOX: XELODA (1000 mg/m$^2$ twice daily for 2 weeks followed by a 7-day rest period) and oxaliplatin (130 mg/m$^2$ as a 2-hour infusion on day 1 every three weeks).

[b]FOLFOX-4: leucovorin (200 mg/m$^2$ as a 2-hour infusion on days 1 and 2 every two weeks), 5-FU (400 mg/m$^2$ as a bolus injection, 600 mg/m$^2$ as a 22 hour infusion on days 1 and 2 every two weeks), and oxaliplatin (85 mg/m$^2$ as a 2 hour infusion on day 1 every two weeks).

## Less Common Clinical Trial Adverse Drug Reactions

Rare or uncommon clinically relevant adverse reactions reported in <5% of metastatic colorectal cancer patients treated with XELODA in combination with oxaliplatin (second-line), 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.

**Gastrointestinal:** intestinal obstruction (2%)
**Nervous:** peripheral motor neuropathy (<1%), encephalopathy (<1%)
**Blood & Lymphatic:** febrile neutropenia (<1%), pancytopenia (<1%)
**Respiratory:** pulmonary embolism (<1%), laryngospasm (<1%), bronchospasm (<1%)
**Vascular:** thrombosis (<1%), deep vein thrombosis (<1%), embolism (<1%)

**Psychiatric:** anxiety (<1%)
**Renal & urinary:** renal failure acute (<1%)
**Hepatobiliary:** hepatic failure (<1%)
**Cardiac:** myocardial infarction (<1%)

**Breast Cancer, XELODA Monotherapy**
The following data (Table 5) are for the study in stage IV breast cancer patients who received a dose of 2500 mg/m$^2$ administered daily for 2 weeks followed by a 1-week rest period. The mean duration of treatment was 121 days. A total of 71 patients (13%) discontinued treatment because of adverse events/intercurrent illness.

**Table 5 XELODA Monotherapy: Percent Incidence of Adverse Reactions in ≥5% of Patients Participating in the Phase II Trial in Stage IV Breast Cancer**

| Body System/ Adverse Event | NCIC Grade | | |
|---|---|---|---|
| | 1 to 4 | 3 | 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 | - |
| Dermatitis | 37 | 1 | - |
| Nail disorder | 7 | - | - |
| **General** | | | |
| Fatigue | 41 | 8 | - |
| Pyrexia | 12 | 1 | - |
| Pain in limb | 6 | 1 | - |
| **Neurological** | | | |
| Paraesthesia | 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 | - |
| **Blood** | | | |
| Neutropenia | 26 | 2 | 2 |
| Thrombocytopenia | 24 | 3 | 1 |
| Anemia | 72 | 3 | 1 |

| Body System/ Adverse Event | NCIC Grade | | |
|---|---|---|---|
| | 1 to 4 | 3 | 4 |
| Lymphopenia | 94 | 44 | 15 |
| **Hepatobiliary**<br>Hyperbilirubinemia | 22 | 9 | 2 |

* Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome (grade 2 and above) can eventually lead to loss of fingerprints (see WARNINGS AND PRECAUTIONS).

**Locally advanced and/or Metastatic Breast Cancer, Combination with Docetaxel**

The following data (Table 6) are for the combination study with XELODA and docetaxel in patients with locally advanced and/or metastatic breast cancer. In the XELODA -Docetaxel combination arm, the treatment was XELODA administered orally 1250 mg/m$^2$ twice daily as intermittent therapy (2 weeks of treatment followed by one week without treatment) for at least 6 weeks and docetaxel administered as a 1 hour intravenous infusion at a dose of 75 mg/m$^2$ on the first day of each 3 week cycle for at least 6 weeks. In the monotherapy arm, docetaxel was administered as a 1 hour intravenous infusion at a dose of 100 mg/m$^2$ on the first day of each 3 week cycle for at least 6 weeks. The mean duration of treatment was 129 days in the combination arm and 98 days in the monotherapy arm. A total of 66 patients (26%) in the combination arm and 49 (19%) in the monotherapy arm withdrew from the study because of adverse events. The percentage of patients requiring dose reductions due to adverse events were 65% in the combination arm and 36% in the monotherapy arm. The hospitalization rate for treatment-related adverse events was 28.7% in the combination arm and 26.3% in the monotherapy arm.

**Table 6 Per Cent Incidence of Adverse Reactions in ≥5% of Patients Participating in the Combination Study of XELODA and Docetaxel in Metastatic Breast Cancer**

| Adverse Event | XELODA 1250 mg/m2/bid (Intermittent Regimen)with Docetaxel 75 mg/m2/3 weeks (n=251) | | | Docetaxel 100 mg/m2/3 weeks (n=255) | | |
|---|---|---|---|---|---|---|
| Body System/Adverse Event | NCIC Grade | | | | | |
| | Total % | Grade 3 % | Grade 4 % | Total % | Grade 3 % | Grade 4 % |
| **GI** | | | | | | |
| Stomatitis | 67 | 17.1 | 0.4 | 43 | 4.7 | - |
| Diarrhea | 64 | 13.5 | 0.4 | 45 | 5.4 | 0.4 |
| Nausea | 43 | 6.4 | - | 35 | 2.0 | - |
| Vomiting | 33 | 3.6 | 0.8 | 22 | 0.8 | - |
| Constipation | 14 | 1.2 | - | 12 | - | - |
| Abdominal pain | 14 | 2.0 | - | 9 | 0.8 | - |
| Dyspepsia | 12 | - | - | 5 | 0.4 | - |
| Abdominal Pain Upper | 9 | - | - | 6 | - | - |
| Dry mouth | 5 | 0.4 | - | 4 | - | - |

| Adverse Event | XELODA 1250 mg/m2/bid (Intermittent Regimen)with Docetaxel 75 mg/m2/3 weeks (n=251) | | | Docetaxel 100 mg/m2/3 weeks (n=255) | | |
|---|---|---|---|---|---|---|
| **Body System/Adverse Event** | **NCIC Grade** | | | | | |
| | **Total %** | **Grade 3 %** | **Grade 4 %** | **Total %** | **Grade 3 %** | **Grade 4 %** |
| **Skin and Subcutaneous** | | | | | | |
| Hand-and-Foot Syndrome | 63 | 24.3 | - | 8 | 1.2 | - |
| Alopecia | 41 | 6.0 | - | 42 | 6.7 | - |
| Nail disorder | 14 | 2.0 | - | 15 | - | - |
| Dermatitis | 8 | - | - | 9 | 0.8 | - |
| Rash erythematous | 8 | 0.4 | - | 4 | - | - |
| Nail discolouration | 6 | - | - | 4 | 0.4 | - |
| Onycholysis | 5 | 1.2 | - | 5 | 0.8 | - |
| Pruritis | 2 | - | - | 5 | - | - |
| **General** | | | | | | |
| Pyrexia | 21 | 0.8 | - | 29 | 0.4 | - |
| Asthenia | 23 | 3.2 | 0.4 | 22 | 5.5 | - |
| Fatigue | 21 | 4.4 | - | 25 | 5.1 | - |
| Weakness | 13 | 1.2 | - | 9 | 2.0 | - |
| Pain in limb | 9 | 0.4 | - | 8 | 0.4 | - |
| Lethargy | 6 | - | - | 5 | 1.2 | - |
| Pain | 6 | - | - | 2 | - | - |
| **Neurological** | | | | | | |
| Dysgeusia | 15 | 0.4 | - | 14 | 0.4 | - |
| Headache | 7 | 0.4 | - | 8 | - | - |
| Paraesthesia | 11 | 0.4 | - | 15 | 0.8 | - |
| Dizziness* | 9 | - | - | 6 | 0.4 | - |
| Insomnia | 4 | - | - | 5 | 0.4 | - |
| Peripheral Neuropathy | 5 | - | - | 10 | 0.8 | - |
| Hypoaesthesia | 4 | - | - | 7 | 0.4 | - |
| **Metabolism** | | | | | | |
| Anorexia | 12 | 0.8 | - | 10 | 0.8 | - |
| Appetite Decreased | 10 | - | - | 4 | - | - |
| Dehydration | 8 | 2.0 | - | 5 | 0.4 | 0.4 |
| **Eye** | | | | | | |
| Lacrimation increased | 12 | - | - | 5 | - | - |
| **Musculoskeletal** | | | | | | |
| Arthralgia | 11 | 1.2 | - | 18 | 2.4 | - |
| Myalgia | 14 | 1.6 | - | 24 | 2.0 | - |
| Back pain | 7 | 0.8 | - | 6 | 0.8 | - |
| **Cardiac** | | | | | | |
| Edema lower limb | 14 | 0.8 | - | 12 | 1.2 | - |
| Edema NOS | 4 | - | - | 5 | - | 0.8 |
| Edema peripheral | 4 | - | - | 5 | 0.4 | - |
| **Hematologic** | | | | | | |
| Neutropenia | 17 | 4.8 | 10.8 | 16 | 2.7 | 11.8 |
| Neutropenic fever | 16 | 2.8 | 13.1 | 21 | 4.7 | 16.1 |
| Anaemia | 13 | 2.8 | 0.8 | 11 | 3.9 | - |

| Adverse Event | XELODA 1250 mg/m2/bid (Intermittent Regimen)with Docetaxel 75 mg/m2/3 weeks (n=251) | | | Docetaxel 100 mg/m2/3 weeks (n=255) | | |
|---|---|---|---|---|---|---|
| **Body System/Adverse Event** | **NCIC Grade** | | | | | |
| | **Total %** | **Grade 3 %** | **Grade 4 %** | **Total %** | **Grade 3 %** | **Grade 4 %** |
| **Respiratory** | | | | | | |
| Dyspnea | 7 | 0.8 | - | 9 | 0.4 | - |
| Cough | 6 | 0.4 | - | 9 | - | - |
| Sore throat | 11 | 1.6 | - | 7 | 0.4 | - |
| Epistaxis | 5 | 0.4 | - | 5 | - | - |
| **Infections and Infestations** | | | | | | |
| Oral Candidiasis | 6 | 0.4 | - | 7 | 0.4 | - |

- Not observed or applicable.
* Excluding vertigo

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

**Gastrointestinal:** hemorrhoids (0.39), ileus (0.39), necrotizing enterocolitis (0.39), esophageal ulcer (0.39), hemorrhagic diarrhea (0.80)
**General:** rigors (0.39), injection site infection (0.39), neuralgia (0.39)
*Neurological:* ataxia (0.39), syncope (1.20), taste loss (0.80), polyneuropathy (0.39), migraine (0.39)
**Cardiac:** supraventricular tachycardia (0.39)
**Infection:** neutropenic sepsis (2.39), lower respiratory tract infection NOS (0.39), pharyngitis (0.39), otitis media (0.39), sepsis (0.39), bronchopneumonia (0.39)
**Blood and Lymphatic:** agranulocytosis (0.39), prothrombin decreased (0.39)
**Vascular:** hypotension (1.20), venous phlebitis & thrombophlebitis (0.39), blood pressure increase (0.39), postural hypotension (0.80)
**Renal:** renal failure (0.39)
**Hepatobiliary:** jaundice (0.39), abnormal liver function tests (0.39), hepatic failure (0.39), hepatic coma (0.39), hepatotoxicity (0.39)
**Immune System:** hypersensitivity (1.20)

**XELODA Monotherapy Metastatic Breast and Colorectal Cancer**
Listed below by body system are the clinical adverse events in <5% of 875 patients (phase III colorectal studies - 596 patients, phase II colorectal study - 34 patients, phase II breast cancer monotherapy studies - 245 patients) reported as related to the administration of XELODA and that were clinically at least remotely relevant.
In parentheses is the incidence of grade 3 or 4 occurrences of each adverse event.

***Gastrointestinal:*** abdominal distension, esophagitis (0.2), intestinal obstruction (0.3), dysphagia, proctalgia, hemorrhoids, fecal abnormality, tongue disorder, ascites (0.1), gastric ulcer (0.1), gastrointestinal hemorrhage (0.2), ileus (0.3), incisional hernia, rectal disorder, swallowing painful, toxic dilation of intestine, melena, gastroenteritis (0.1), flatulence, gastritis, duodenitis, colitis

***Skin and Subcutaneous:*** nail disorder (0.1), sweating increased (0.1), face edema, photosensitivity reaction (0.1), urticaria, skin ulcer, genital pruritus, skin lesion, ecchymoses, hyperkeratosis, intertrigo, leg ulcer (excluding varicose), localized skin reaction, red face, rosacea, scab, foot ulcer (0.1), dry skin (<0.01), localized exfoliation, skin hyperpigmentation, skin fissures (< 0.02)

***General:*** shivering, chest pain (0.2), influenza-like illness, hot flushes, palmar erythema, hiccups, pain (0.1), hoarseness, fluid retention, irritability, difficulty in walking, thirst, chest mass, collapse, fibrosis (0.1), hemorrhage, neck edema, sedation, sudden death unexplained (0.1), swelling, ulcer (0.1)

***Neurological:*** insomnia, ataxia (0.5), sedation, syncope (0.1), tremor, dysphasia, encephalopathy (0.1), coordination abnormal, dysarthria, facial palsy, loss of consciousness (0.2), mental impairment, myoclonic jerks, peroneal nerve palsy (0.1), headache (0.5)

***Metabolism:*** weight increase, malnutrition (0.2), appetite increased, food intolerance (0.1), hypertriglyceridemia (0.1), hypokalemia, diabetes control impaired (0.1), hypomagnesemia

***Eye:*** vision abnormal, cataract

***Respiratory:*** cough (0.1), epistaxis (0.1), sore throat, chest tightness, rhinitis, increased sputum production, bronchospasm (0.2), hemoptysis, nasal ulcer, pneumothorax, crackles, orthopnea, pharyngeal disorder, pleural disorder, respiratory distress (0.1), sneezing

***Cardiac:*** tachycardia (0.1), bradycardia, arrhythmia, chest pain (cardiac) (0.2), atrial fibrillation, cardiac failure, cardiomyopathy, extrasystoles, myocardial/infarction (0.1), myocarditis (0.1), pericardial effusion

***Infection:*** herpes simplex, upper respiratory tract infection (0.1), urinary tract infection (0.2), localized infection, sepsis (0.3), bronchitis (0.1), lower respiratory tract infection, cellulitis, fungal infection (0.3), pneumonia (0.1), bronchopneumonia (0.1), herpes zoster, infection (0.1), influenza, keratoconjunctivitis, laryngitis (0.1), superinfection, immune system compromise, and/or disruption of mucous membranes, such as local and fatal systemic infections (including bacterial, viral, fungal etiologies) and sepsis

***Musculoskeletal:*** myalgia, back pain, arthralgia (0.1), bone pain (0.1), neck pain, arthritis (0.1), calcaneal spur, muscle weakness

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

***Vascular:*** hypotension (0.2), hypertension (0.1), flushing, lymphoedema (0.1), hematoma, pulmonary embolism (0.2), cerebrovascular accident (0.1), transient ischemic attack, varicose veins, venous thrombosis (0.8)

***Psychiatric****:* depression, confusion (0.1), amnesia, libido decreased, loss of confidence, mood alteration, personality change, psychogenic disorder

***Renal:*** dysuria, urinary incontinence, hematuria, hydronephrosis (0.1), nocturia (0.1), urinary tract disorder, urine discolouration, polyuria, renal impairment (0.1), urinary retention

***Reproductive System:*** intermenstrual bleeding, balanoposthitis, vaginal pain, nipple disorder, premenstrual tension syndrome

***Ear:*** vertigo, earache, deafness, sensation of block in ear
***Hepatobiliary:*** jaundice (0.3), hepatomegaly, hepatic pain, fatty liver, bile duct stone (0.1), hepatic fibrosis (0.1), hepatitis (0.1), hepatic cholestatic (0.1)
***Injury and Poisoning:*** radiation recall syndrome (0.1), bruising, overdose, scratch
***Surgical:*** paronychia drainage, postoperative complications, wound drainage increased
***Immune System:*** food allergy, hypersensitivity (0.1)
***Endocrine:*** cushingoid, hypothyroidism, hirsutism
***Neoplasms:*** lipoma, solar keratosis (0.1)

The following table (Table 7) displays laboratory abnormalities observed in 949 patients, regardless of relationship to treatment with XELODA in metastatic breast and colorectal cancer.

**Table 7 Laboratory Abnormalities[a]: XELODA Monotherapy in Metastatic Breast and Colorectal Cancer.**

| | **XELODA 1250 mg/m$^2$ twice daily intermittent N=949** | | | |
|---|---|---|---|---|
| **Parameter[a]** | **Patients with Grade 3 / 4 abnormality (%)** | **Patients with worsening from baseline of any grade (%)** | **Patients with worsening from baseline by 1 or 2 grades (%)** | **Patients with worsening from baseline by 3 or 4 grades (%)** |
| Decreased hemoglobin | 3.1 | 41.4 | 40.7 | 0.7 |
| Decreased neutrophils | 3.6 | 18.7 | 15.6 | 3.1 |
| Decreased granulocytes | 0.2 | 1.9 | 1.7 | 0.2 |
| Decreased lymphocytes | 44.4 | 58.2 | 53.1 | 5.1 |
| Decreased platelets | 2.0 | 20.4 | 18.8 | 1.6 |
| Increased bilirubin | 17.7 | 36.9 | 21.6 | 15.3 |
| Increased ALAT (SGPT) | 0.5 | 16.7 | 16.3 | 0.4 |
| Increased ASAT (SGOT) | 1.1 | 25.1 | 24.8 | 0.3 |
| Increased serum creatinine | 0.5 | 9.8 | 9.4 | 0.4 |
| Increased alkaline phosphatase | 3.5 | 27.2 | 27.2 | 0.0 |
| Hyperglycemia | 4.4 | 40.1 | 39.2 | 0.9 |

[a] Laboratory abnormalities were graded according to the categories of the NCIC CTC Grading System.

## Adverse Events Occurring in Special Patient Populations in Clinical Trials with XELODA Monotherapy in the Metastatic Setting

***Geriatrics:*** Among the 21 patients (80 years of age and greater) with either metastatic breast or colorectal cancer who received XELODA monotherapy (N=875), 6 (28.6%), 3 (14.3%), and 2 (9.5%) patients experienced reversible grade 3/4 diarrhea, nausea and vomiting, respectively. Among the 496 patients aged 60 to 79 years old, the incidence of gastrointestinal toxicity was similar to that in the overall population. Patients 70 to 79 years old (22%) had a higher incidence of hand-and-foot syndrome.

***Hyperbilirubinemia:*** In 875 patients with either metastatic breast or colorectal cancer who received at least one dose of capecitabine 2500 mg/m$^2$ daily for 2 weeks followed by a 1-week

rest period, grade 3 hyperbilirubinemia occurred in 133 (15.2%) and grade 4 hyperbilirubinemia occurred in 34 (3.9%) patients. Grade 3/4 hyperbilirubinemia occurred in 22.8% of the 566 patients with hepatic metastases and in 12.3% of the 309 patients without hepatic metastases at baseline. Of the 167 patients with grade 3 or 4 hyperbilirubinemia, 31 (18.6%) also had post-baseline elevations (grades 1 to 4, without elevations at baseline) in alkaline phosphatase and 46 (27.5%) had post-baseline elevations in transaminases at any time (not necessarily concurrent). The majority of these patients, 20 (64.5%) and 33 (71.7%), had liver metastases at baseline. In addition, 96 (57.5%) and 59 (35.3%) of the 167 patients had elevations (grades 1 to 4) at both pre- and post-baseline in alkaline phosphatase or transaminases, respectively. Only 13 (7.8%) and 5 (3.0%) had grade 3 or 4 elevations in alkaline phosphatase or transaminases.

## Postmarketing Reports of Adverse Events

The following additional adverse events have been identified during post-marketing use of XELODA. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to XELODA exposure.

**Table 8 Adverse Drug Reactions Reported in the Post Marketing Setting**

| System Organ Class (SOC) | ADR(s) |
|---|---|
| **Gastrointestinal** | Serious gastro-intestinal disorders have been reported in patients exposed to XELODA and include but are not limited to: necrotizing enterocolitis, ileus paralytic, gastrointestinal perforation and intestinal obstruction. |
| **Cardiovascular** | Thromboembolic events such as deep vein thrombosis, thrombophlebitis and pulmonary embolism have been reported. |
| **Hepatobiliary disorders** | Hepatic failure, Cholestatic hepatitis. |
| **Renal and urinary disorders** | Acute renal failure secondary to dehydration including fatal outcome (see WARNINGS AND PRECAUTIONS). |
| **Immune** | Cutaneous lupus erythematosus, severe skin reactions such as Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (see WARNINGS AND PRECAUTIONS) |
| **Eye disorders** | Lacrimal duct stenosis NOS, Corneal disorders including keratitis. |
| **Nervous system disorders** | Toxic leukoencephalopathy (see WARNINGS AND PRECAUTIONS). |

## Exposure to crushed or cut XELODA tablets

In the instance of exposure to crushed or cut XELODA tablets, the following ADRs have been reported: eye irritation, eye swelling, skin rash, headache, paresthesia, diarrhea, nausea, gastric irritation, and vomiting.

## DRUG INTERACTIONS

### Drug-Drug Interactions

**Sorivudine and analogues[4]:** A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine, has been described. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, capecitabine must not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine. There must be at least a 4-week waiting period between end of treatment with sorivudine or its chemically related analogues such as brivudine and start of capecitabine therapy.

**Phenytoin and Fosphenytoin**: Increased phenytoin plasma concentrations have been reported during concomitant use of XELODA with phenytoin, suggesting a potential interaction. Formal drug-drug interactions studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP 2C9 isoenzyme system by capecitabine (see subsection below, Cytochrome P450 2C9 Substrates). Patients taking phenytoin or fosphenytoin concomitantly with XELODA should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

**Coumarin Anticoagulants:** 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. In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC (+57%) of S-warfarin. These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. In a clinical interaction study, after a single 20 mg dose of warfarin, XELODA treatment increased the AUC of S-warfarin by 57% with a 91% increase in INR value. Patients taking coumarin-derivative anticoagulants concomitantly with XELODA should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anticoagulant dose adjusted accordingly.

**Cytochrome P450 2C9 Substrates:** No formal drug-drug interaction studies with capecitabine and other drugs known to be metabolized by the cytochrome P450 2C9 isoenzyme have been conducted. Care should be exercised when XELODA is co-administered with these drugs, which are metabolized by cytochrome P450 2C9 such as for example warfarin or phenytoin. Patients receiving concomitant XELODA and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly. Patients taking phenytoin concomitantly with XELODA should be regularly monitored for increased phenytoin plasma concentrations.

[4] sorivudine and its chemically related analogues, such as brivudine are not authorized for sale in Canada.

**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).

**Leucovorin:** A phase I study evaluating the effect of leucovorin on the pharmacokinetics of capecitabine was conducted in 22 cancer patients. Leucovorin has no effect on the pharmacokinetics of capecitabine and its metabolites; however, the toxicity of capecitabine may be enhanced by leucovorin.

**Oxaliplatin:** No clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occurred when capecitabine and oxaliplatin were administered in combination.

**Drug-Food Interactions**

The effect of food on the pharmacokinetics of capecitabine was investigated in 11 cancer patients. The rate and extent of absorption of capecitabine is decreased when administered with food. The effect on $AUC_{0-\infty}$ of the 3 main metabolites in plasma (5'DFUR, 5-FU, FBAL) is minor. In all clinical trials, patients were instructed to take XELODA within 30 minutes after a meal. Therefore, since current safety and efficacy data are based upon administration with food, it is recommended XELODA be administered with food.

## DOSAGE AND ADMINISTRATION

**Dosing Considerations**

XELODA is intended for long-term administration unless clinically inappropriate. XELODA tablets should be swallowed whole with water within 30 minutes after a meal. XELODA tablets should not be crushed or cut (see ADVERSE REACTIONS, Postmarketing Reports of Adverse Events). If patients cannot swallow XELODA tablets whole and tablets must be crushed or cut, this should be done by a professional trained in the safe handling of cytotoxic drugs (see SPECIAL HANDLING INSTRUCTIONS).

**Recommended Dose and Dosage Adjustment**

**Monotherapy:** The recommended dose of XELODA (capecitabine) is 1250 mg/m$^2$ administered twice daily (morning and evening; equivalent to 2500 mg/m$^2$ total daily dose) for 14 days followed by a seven day rest period.

For adjuvant treatment of stage III colon cancer, XELODA is intended to be given for a total of 8 cycles (or 24 weeks).

**Colorectal Cancer, Combination Therapy with Oxaliplatin:**

In combination with oxaliplatin the recommended dose of XELODA is 1000 mg/m$^2$ twice daily for 2 weeks followed by a 7-day rest period. The first dose of XELODA is given on the evening

of day 1 and the last dose is given on the morning of day 15. Given as a 3-weekly schedule, oxaliplatin is administered as a 130 mg/m$^2$ intravenous infusion over 2 hours.

Premedication to maintain adequate anti-emesis according to the oxaliplatin Product Monograph should be started prior to oxaliplatin administration for patients receiving the XELODA plus oxaliplatin combination

**Locally advanced and/or Metastatic Breast Cancer, Combination Therapy with Docetaxel:** In combination with docetaxel, the recommended starting dose of XELODA is 1250 mg/m$^2$ twice daily for 2 weeks followed by a 7-day rest period combined with docetaxel 75 mg/m$^2$ administered as a 1-hour intravenous infusion every 3 weeks (see ACTIONS AND CLINICAL PHARMACOLOGY, CLINICAL TRIALS, Breast Carcinoma). Premedication according to the docetaxel labelling, should be started prior to docetaxel administration for patients receiving the XELODA plus docetaxel combination.

**Dose calculation**

XELODA dose is calculated according to body surface area. Tables 9 and 10 show examples of the standard and reduced dose calculations for a XELODA starting dose of either1250 mg/m$^2$ or 1000 mg/m$^2$.

**Table 9 Standard and reduced dose calculations according to body surface area for a starting XELODA dose of 1250 mg/m$^2$**

| | **Dose level 1250 mg/m$^2$ (twice daily)** | | | | |
|---|---|---|---|---|---|
| | **Full dose**<br><br>**1250 mg/m$^2$** | **Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)** | | **Reduced dose (75%)**<br><br>**950 mg/m$^2$** | **Reduced dose (50%)**<br><br>**625 mg/m$^2$** |
| **Body Surface Area (m$^2$)** | **Dose per administration (mg)** | **150 mg** | **500 mg** | **Dose per administration (mg)** | **Dose per administration (mg)** |
| **≤ 1.26** | 1500 | - | 3 | 1150 | 800 |
| **1.27 - 1.38** | 1650 | 1 | 3 | 1300 | 800 |
| **1.39 - 1.52** | 1800 | 2 | 3 | 1450 | 950 |
| **1.53 - 1.66** | 2000 | - | 4 | 1500 | 1000 |
| **1.67 - 1.78** | 2150 | 1 | 4 | 1650 | 1000 |
| **1.79 - 1.92** | 2300 | 2 | 4 | 1800 | 1150 |
| **1.93 - 2.06** | 2500 | - | 5 | 1950 | 1300 |
| **2.07 - 2.18** | 2650 | 1 | 5 | 2000 | 1300 |

| | Dose level 1250 mg/m$^2$ (twice daily) | | | | |
|---|---|---|---|---|---|
| | **Full dose**<br><br>**1250 mg/m$^2$** | **Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)** | | **Reduced dose (75%)**<br><br>**950 mg/m$^2$** | **Reduced dose (50%)**<br><br>**625 mg/m$^2$** |
| **≥ 2.19** | 2800 | 2 | 5 | 2150 | 1450 |

**Table 10 Standard and reduced dose calculations according to body surface area for a starting XELODA dose of 1000 mg/m$^2$**

| | Dose level 1000 mg/m$^2$ (twice daily) | | | | |
|---|---|---|---|---|---|
| | **Full dose**<br><br>**1000 mg/m$^2$** | **Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)** | | **Reduced dose (75%)**<br><br>**750 mg/m$^2$** | **Reduced dose (50%)**<br><br>**500 mg/m$^2$** |
| **Body Surface Area (m$^2$)** | **Dose per administration (mg)** | **150 mg** | **500 mg** | **Dose per administration (mg)** | **Dose per administration (mg)** |
| **≤ 1.26** | 1150 | 1 | 2 | 800 | 600 |
| **1.27 - 1.38** | 1300 | 2 | 2 | 1000 | 600 |
| **1.39 - 1.52** | 1450 | 3 | 2 | 1100 | 750 |
| **1.53 - 1.66** | 1600 | 4 | 2 | 1200 | 800 |
| **1.67 - 1.78** | 1750 | 5 | 2 | 1300 | 800 |
| **1.79 - 1.92** | 1800 | 2 | 3 | 1400 | 900 |
| **1.93 - 2.06** | 2000 | - | 4 | 1500 | 1000 |
| **2.07 - 2.18** | 2150 | 1 | 4 | 1600 | 1050 |
| **≥ 2.19** | 2300 | 2 | 4 | 1750 | 1100 |

**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.

For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening, treatment can be continued at the same dose without reduction or interruption.

Dose modifications for the use of XELODA are shown in Table 11.

**Table 11 Recommended Dose Modifications for XELODA**

| Toxicity NCIC Grade* | 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 | |
| **Grade 4** | | |
| -1st appearance | Discontinue permanently<br>*or*<br>If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1 | 50% |
| -2nd appearance | Discontinue permanently | |

* According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (Version 1 or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. For Hand-and-Foot Syndrome and hyperbilirubinemia (see WARNINGS AND PRECAUTIONS)

Dosage modifications are not recommended for grade 1 events. Therapy with XELODA should be interrupted upon the occurrence of a grade 2 or 3 adverse experience. Once the adverse event has resolved or decreased in intensity to grade 1, then XELODA therapy may be restarted at full dose or as adjusted according to Table 11 for XELODA monotherapy. If a grade 4 event 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. Patients taking XELODA should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of XELODA omitted for toxicity are not replaced.

**Haematology:** Patients with baseline neutrophil counts of $<1.5 \times 10^9$/L and/or thrombocyte counts of $<100 \times 10^9$/L should not be treated with XELODA. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 haematologic toxicity, treatment with XELODA should be interrupted.

**Combination Therapy:** Dose modifications for toxicity when XELODA is used in combination with other therapies should be made according to Table 11 above for XELODA and according to the appropriate Product Monograph for the other agent(s).

At the beginning of a treatment cycle, if a treatment delay is indicated for either XELODA or the other agent(s), then administration of all agents should be delayed until the requirements for restarting all drugs are met.

During a treatment cycle for those toxicities considered by the treating physician not to be related to XELODA, XELODA should be continued and the dose of the other agent adjusted according to the appropriate Product Monograph.

If the other agent(s) have to be discontinued permanently, XELODA treatment can be resumed when the requirements for restarting XELODA are met.

This advice is applicable to all indications and to all special populations.

**Adjustment of Starting Dose in Special Populations**

**Hepatic Impairment:** In patients with mild to moderate hepatic dysfunction due to liver metastases, no dose adjustment is necessary. Patients with severe hepatic dysfunction have not been studied (see WARNINGS AND PRECAUTIONS).

**Renal Impairment:** In patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min [Cockroft and Gault]) at baseline, a dose reduction to 75% from a starting dose of 1250 mg/m$^2$ is recommended based upon pharmacokinetic and safety data (see ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Renal Insufficiency, and WARNINGS AND PRECAUTIONS). In patients with mild renal impairment (calculated creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. In patients with severe renal impairment, XELODA should not be administered (see CONTRAINDICATIONS). Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event, with subsequent dose adjustment as outlined in the tables above. If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, XELODA should be discontinued. The dose adjustment recommendation for patients with moderate renal impairment applies both to monotherapy and combination use. For dosage calculations, see Table 9.

**Geriatrics**: No adjustment of the starting dose is needed for XELODA. However for XELODA monotherapy in the metastatic setting, severe Grade 3 or 4 treatment-related adverse events were more frequent in patients over 80 years of age compared to younger patients. Careful monitoring of elderly patients is advisable.

When XELODA was used in combination with other agents, elderly patients (≥ 65 years) experienced more grade 3 and grade 4 adverse drug reactions (ADRs) and ADRs that led to discontinuation, than younger patients. Careful monitoring of elderly patients is advisable.

For treatment with XELODA in combination with docetaxel, an increased incidence of Grade 3 or 4 treatment-related adverse events and treatment-related serious adverse events was observed in patients 60 years of age or more.

## OVERDOSAGE

The manifestations of acute overdose include: nausea, vomiting, diarrhea, mucositis, GI irritation and bleeding, and bone marrow depression. Management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

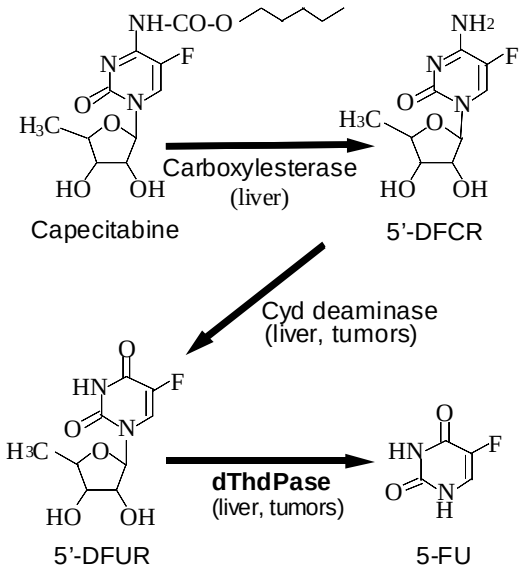
## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Capecitabine is a tumour- activated antineoplastic agent (antimetabolite) belonging to the novel fluoropyrimidine carbamate class. It was rationally designed as an orally administered precursor of 5'-deoxy-5-fluorouridine (5'-DFUR). Capecitabine is selectively activated to the cytotoxic moiety, 5-fluorouracil (5-FU), by thymidine phosphorylase in tumours.

Within normal and tumour cells, 5-FU is further metabolized to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP) which cause cell injury by both DNA and RNA-derived mechanisms (see the DETAILED PHARMACOLOGY section for more information).

**Bioactivation:** Capecitabine is absorbed unchanged from the gastrointestinal tract, metabolized primarily in the liver by the 60kDa carboxylesterase to 5’-Deoxy-5-fluorocytidine (5’-DFCR) which is then converted to 5’-DFUR by cytidine deaminase, principally located in the liver and tumour tissue. Further metabolism of 5’-DFUR to the pharmacologically-active agent 5-FU occurs mainly at the site of the tumour by thymidine phosphorylase (dThdPase), which has levels considerably higher in tumour tissues compared to normal tissues (see the following figure for the metabolic pathway of capecitabine). Healthy liver tissues also contain a relatively high activity of dThdPase. In human cancer xenograft models, capecitabine demonstrated a synergistic effect in combination with docetaxel which may be related to the upregulation of thymidine phosphorylase by docetaxel.




## Pharmacokinetics

**Pharmacokinetic Parameters:** Table 12 below shows the pharmacokinetic parameters of capecitabine, 5'-DFCR, 5'-DFUR and 5-FU in plasma at steady-state (day 14) following administration of the recommended dose (1255 mg/m$^2$ b.i.d.) in 8 cancer patients. The peak of plasma concentrations of intact drug, 5'-DFCR, 5'-DFUR and 5-FU is reached rapidly and then concentrations decline with a short half-life for all species.

**Table 12 Descriptive Statistics on the Pharmacokinetic Parameters Estimated on Day 14 after Administration of Capecitabine (1255 mg/m$^2$) in 8 Cancer Patients**

| Parameter | Capecitabine | 5'-DFCR | 5'-DFUR | 5-FU | $FUH_2$ | FBAL |
|---|---|---|---|---|---|---|
| $C_{max}$ (µg/mL) | 3.99 (56%) | 1.71 (236%) | 9.37 (94%) | 0.709 (87%) | 0.442 (103%) | 5.32 (26%) |
| $t_{max}$ (h) | 1.50 (0.78-2.17) | 2.00 (0.78-4.08) | 2.00 (1.28-4.08) | 2.00 (1.28-4.08) | 2.28 (2.00-4.08) | 3.34 (3.00-5.58) |
| $AUC_{0-t}$ (µg.h/mL) | 7.29 (32%) | 3.97 (175%) | 19.9 (57%) | 1.62 (62%) | 1.20 (153%) | 30.0 (20%) |
| $AUC_{0-\infty}$ (µg.h/mL) | 7.40 (34%) | 5.21 (140%) | 21.7 (63%) | 1.63 (74%) | 2.15 (67%) | 35.2 (27%) |
| $t_{1/2}$ (h) | 0.85 (88%) | 1.11 (80%) | 0.66 (17%) | 0.76 (25%) | 1.14 (26%) | 3.23 (40%) |

Geometric means (CV) are reported for $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$. Median values (min-max) are reported for $t_{max}$. Arithmetic means (CV) are reported for $t_{1/2}$.

After oral administration, plasma data indicate an extensive and rapid conversion to the first two metabolites in plasma, 5'-DFCR and 5'-DFUR. The peak plasma concentrations for the drug and its two first metabolites occurs shortly (median $t_{max}$ of 1.50 to 2.0 h) after capecitabine administration. Concentrations then decline exponentially with half-lives of 0.85 h (arithmetic mean), 1.11 h and 0.66 h for intact drug, 5'-DFCR and 5'-DFUR, respectively. Following administration of 1255 mg/m$^2$, a high $AUC_{0-\infty}$ is obtained for 5'-DFUR (geometric mean = 21.7 μg•h/mL, CV = 63%, n = 8). On day 14, the systemic exposure (AUC) to 5-FU is approximately 13 times lower than the systemic exposure to 5'-DFUR.

In plasma, the peak of FBAL concentration occurred approximately 3 h after drug intake. The decline in FBAL concentration is characterized by a half-life of 3.23 ± 1.29 h. Plasma concentrations of FBAL are high (1.6 times those of 5'-DFUR and 22 times those of 5-FU), which probably reflects the extensive formation of 5-FU in the tumour and other tissues.

**Absorption, Distribution, Metabolism and Excretion:** Capecitabine reached peak blood levels in about 1.5 hours ($T_{max}$) with peak 5-FU blood levels occurring slightly later, at 2 hours. Administration with food decreases the rate of capecitabine absorption but only results in a minor decrease in the AUC's of 5'-DFUR and 5-FU (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). Plasma protein binding of capecitabine and its metabolites is low (less than 60%) and is not concentration dependent. Capecitabine was primarily bound to human albumin (approximately 35%). Capecitabine is extensively metabolized 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. Over 70% of the administered capecitabine dose is recovered in urine as drug-related material, about 50% of it as FBAL.

Phase I studies evaluating the effect of XELODA on the pharmacokinetics of either docetaxel or paclitaxel and vice versa showed no effect by XELODA on the pharmacokinetics of docetaxel or paclitaxel ($C_{max}$ and AUC) and no effect by docetaxel or paclitaxel on the pharmacokinetics of 5'-DFUR (the most important metabolite of capecitabine).

**Pharmacokinetics in Colorectal Tumours and Adjacent Healthy Tissue:** Following oral administration of capecitabine (1255 mg/m2 b.i.d. 5 to 7 days) in patients with colorectal cancer, concentrations of 5-FU were significantly greater in primary tumour than in adjacent healthy tissue (geometric mean ratio 2.5; CI:1.5 to 4.1) and in plasma (geometric mean ratio 14).

**Special Populations and Conditions**

A population pharmacokinetic analysis was carried out after XELODA treatment of 505 patients with metastatic colorectal cancer dosed at 2500 mg/m$^2$/day. Gender, race, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, ASAT and ALAT had no statistically-significant effect on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL.

**Geriatrics:** Based on the population pharmacokinetic analysis which included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients greater or equal to 65, age has no influence on the pharmacokinetics of 5'-DFUR and 5-FU. The AUC of FBAL increased with age (20% increase in age results in a 15% increase in the AUC of FBAL). This increase is likely due to a change in renal function (see CLINICAL PHARMACOLOGY: *Renal Insufficiency*). However, the elderly may be pharmacodynamically more sensitive to the toxic effects of 5-FU (see WARNINGS AND PRECAUTIONS, Geriatrics and DOSAGE AND ADMINISTRATION).

**Gender:** Based on population pharmacokinetic analysis including 202 females (40%) and 303 males (60%), gender has no influence on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL.

**Race:**Based on population pharmacokinetic analysis of 455 white patients (90.1%), 22 black patients (4.4%) and 28 patients of other race or ethnicity (5.5%), the pharmacokinetics of black patients were not different compared to white patients. For the other minority groups the numbers were too small to draw a conclusion.

**Hepatic Insufficiency:** Capecitabine has been evaluated in patients with mild to moderate hepatic dysfunction due to liver metastases. Both $C_{max}$ and $AUC_{0-\infty}$ of capecitabine, 5'-DFUR and 5-FU were increased by 49%, 33% and 28% and by 48%, 20% and 15%, respectively. Conversely, $C_{max}$ and AUC of 5'-DFCR decreased by 29% and 35%, respectively. Therefore, bioactivation of capecitabine is not affected. There are no pharmacokinetic data on patients with severe hepatic impairment (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

**Renal Insufficiency:** Based on a pharmacokinetic study in cancer patients with mild to severe renal impairment, there is no evidence for an effect of creatinine clearance on the pharmacokinetics of intact drug and 5-FU. Creatinine clearance was found to influence the systemic exposure to 5'-DFUR (35% increase in AUC when creatinine clearance decreases by 50%) and to FBAL (114% increase in AUC when creatinine clearance decreases by 50%). FBAL is a metabolite without antiproliferative activity; 5'-DFUR is the direct precursor of 5-FU.

As seen with 5-FU, the incidence of related grade 3 or 4 adverse events is higher in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

For more detailed information on the pharmacokinetics of capecitabine, please refer to the DETAILED PHARMACOLOGY section.

## STORAGE AND STABILITY

XELODA tablets should be stored at 15-30ºC and in the original package.

## SPECIAL HANDLING INSTRUCTIONS

### Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

Special handling using appropriate equipment and disposal procedures, should be taken as XELODA is a cytotoxic drug. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

### Composition:

Each XELODA 150 mg and 500 mg tablet contains either 150 mg or 500 mg capecitabine, respectively. Non-medicinal ingredients (alphabetical order): croscarmellose sodium, hydroxypropyl methylcellulose, iron oxides (yellow and red), lactose anhydrous, magnesium stearate, microcrystalline cellulose, talc, titanium dioxide.

### Availability:

XELODA is available as a film-coated tablet in strengths of either 150 mg or 500 mg.

XELODA 150 mg tablets are light peach-coloured, biconvex, film-coated, oblong-shaped tablets with XELODA engraved on one side and 150 on the reverse. XELODA 150 mg tablets are available in HDPE bottles containing 60 tablets or in blister packs containing 60 tablets (10 tablets per blister card and 6 blister cards per carton).

XELODA 500 mg tablets are peach- coloured, biconvex, film-coated, oblong-shaped tablets with XELODA engraved on one side and 500 on the reverse. XELODA 500 mg tablets are available in HDPE bottles containing 120 tablets or in blister packs containing 120 tablets (10 tablets per blister card and 12 blister cards per carton).

## PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

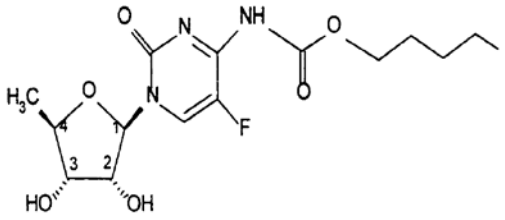
### Drug Substance

Proper name: capecitabine

Chemical name: 5'-Deoxy-5-fluoro-N-[(pentyloxy)carbonyl]-cytidine

Molecular formula and molecular weight: $C_{15}H_{22}FN_3O_6$; 359.35

Structural formula:




Physicochemical properties:

| | |
|---|---|
| Physical Form: | white to off-white crystalline powder |
| Solubility: | Water 2.6 g/100 mL |
| pKa: | 8.8 (in water and titrated with 0.1 N KOH with bubbling $N_2$) |
| Partition co-efficient: | octanol/buffer: log P =4.4-0.98 (range for pH 5.0-9.5) |
| Melting Point: | 120°C with decomposition |

## CLINICAL TRIALS

In a phase I study with XELODA, the maximum-tolerated dose as a single agent in the treatment of patients with solid tumours 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 leucopenia.

### Colorectal Carcinoma:

### Adjuvant Colon Cancer

Data from one open-label, multicenter, randomized, controlled, non-inferiority, phase III clinical trial in patients with stage III (Dukes C) colon cancer supports the use of XELODA for the adjuvant treatment of patients with stage III colon cancer (X-ACT Study: M66001). In this trial, 1987 patients were randomized to treatment with monotherapy XELODA (1250 mg/m$^2$ twice daily for 2 weeks followed by a 1-week rest period and given as 3-week cycles for 24 weeks) (N=1004) or 5-FU and leucovorin (Mayo regimen: 20 mg/m$^2$ leucovorin i.v. followed by 425 mg/m$^2$ i.v. bolus

5-FU, on days 1 to 5, every 28 days for 24 weeks) (N=983). Although this trial used bolus 5-FU in the control arm, infusional 5-FU has been shown to be superior to bolus 5-FU.

The primary efficacy endpoint was disease-free survival. The original conditional approval was based on primary analysis at a median follow-up time of 3.8 years which showed. XELODA was at least equivalent to i.v. 5-FU/LV in disease-free survival (p=0.0001, non-inferiority margin 1.2) with a trend towards superiority in disease-free survival. The full approval was based on an updated analysis at a median follow-up time of 6.9 years which confirmed XELODA to be at least equivalent to 5-FU/LV in disease-free survival although there was no longer a trend toward superiority in disease-free survival (p=0.06). A summary of the results is provided in Table 13. Compared with 5-FU/LV, XELODA was associated with lower incidence of stomatitis, neutropenia and febrile neutropenia but with a considerably higher incidence of hand-and-foot syndrome and hyperbilirubinemia in the adjuvant treatment of patients with Dukes Stage C colon cancer.

**Figure 1: Kaplan-Meier Estimates of Disease-free Survival (All Randomized Population)**

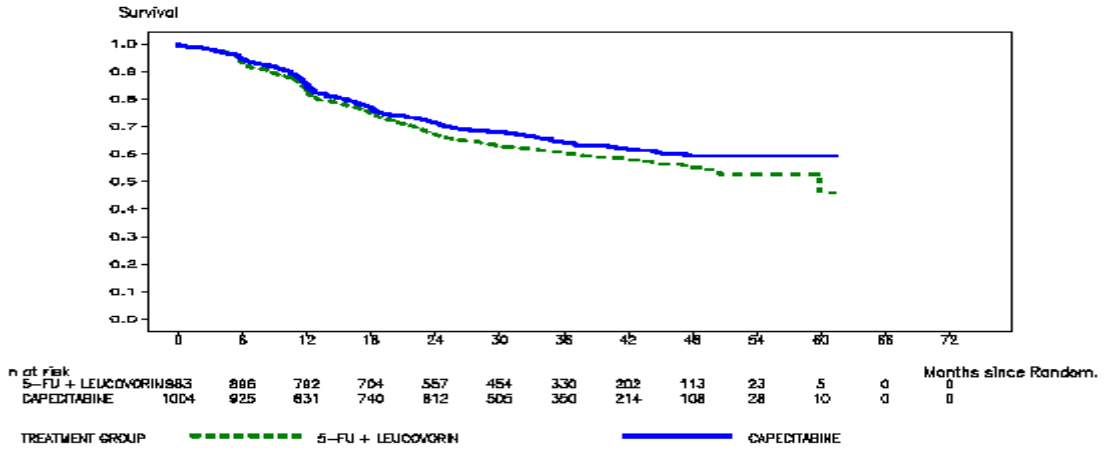



**Table 13 Efficacy of XELODA vs 5-FU/LV in Adjuvant Treatment of stage III**

## (Dukes Stage C) Colon Cancer

| Design | Drug/Dosage | No. of Patients Enrolled -Demographic Data | Results of Primary Analysis – median follow-up 3.8 years | Results of Updated Analysis –median follow-up 6.9 years |
|---|---|---|---|---|
| **PIVOTAL PHASE III STUDY (X-ACT Study)**<br><br>randomized, controlled, multicenter<br><br>patients with stage III (Dukes' stage C) colon cancer | capecitabine 2500 mg/m$^2$/day for 2 weeks with a 1 week rest period [given as 3 week cycles for a total of 8 cycles (24 weeks)]<br><br>5-FU/leucovorin (LV) Mayo regimen - 20 mg/m$^2$ leucovorin I.V. followed by 425 mg/m$^2$ I.V. bolus 5-FU on days 1 to 5, every 28 days [given as 4 week cycles for a total of 6 cycles (24 weeks)] | N=1004<br>Age (yrs) - Md: 62; range: 25 - 80<br>M/F: 542(54%)/ 461(46%)<br>ECOG Score: 0 (%) 849 (85)<br>1 (%) 152 (15)<br>Node Status[a] : N1 (%) 695 (69)<br>N2 (%) 305 (30)<br>Other (%) 4 (0.4)<br><br>N=983<br>Age (yrs) - Md: 63; range: 22 - 82<br>M/F: 532(54%)/ 451 (46%)<br>ECOG Score: 0 (%) 830 (85)<br>1 (%) 147 (15)<br>Node Status[a]: N1 (%) 694 (71)<br>N2 (%) 288 (29)<br>Other (%) 1 (0.1) | **All Randomized Population:**<br>Disease-Free Survival Hazard Ratio[b] = 0.87 (95% C.I. 0.75-1.00); p[c] = 0.053<br><br>3-year disease-free survival rate<br>capecitabine - 64%<br>5-FU/LV - 61%<br><br>Overall Survival Hazard Ratio[b] = 0.84 (95% C.I. 0.69-1.01; p[c] = 0.071)<br><br>3-year overall survival rate<br>capecitabine - 81%<br>5-FU/LV - 78%<br><br>**Per Protocol Population:**<br>Disease-Free Survival Hazard Ratio[b] = 0.89 (95% C.I. 0.76-1.04); p[c] = 0.157<br><br>3-year disease free survival rate<br>capecitabine - 65%<br>5-FU/LV - 63%<br><br>Overall Survival Hazard Ratio[b] = 0.90 (95% C.I. 0.73-1.10); p[c] = 0.298<br><br>3-year overall survival rate<br>capecitabine – 83%<br>5-FU/LV – 80% | **All Randomized Population:**<br>Disease-Free Survival Hazard Ratio[b] = 0.88 (95% C.I. 0.77-1.01); p[c] = 0.068<br><br>5-year disease-free survival rate<br>capecitabine – 60.8%<br>5-FU/LV – 56.7%<br><br>Overall Survival Hazard Ratio[b] = 0.86 (95% C.I. 0.69-1.01; p[c] = 0.060)<br><br>5-year overall survival rate<br>capecitabine – 71.4%<br>5-FU/LV – 68.4%<br><br>**Per Protocol Population:**<br>Disease-Free Survival Hazard Ratio[b] = 0.92 (95% C.I. 0.80-1.06); p[c] = 0.2743<br><br>5-year disease free-survival rate<br>capecitabine – 60.9%<br>5-FU/LV – 58.4%<br><br>Overall Survival Hazard Ratio[b] = 0.93 (95% C.I. 0.73-1.09); p[c] = 0.357<br><br>5-year overall survival rate<br>capecitabine – 72%<br>5-FU/LV – 70.5% |

[a]N1- tumor in 1-3 regional lymph nodes; N2- tumor in ≥ 4 regional lymph nodes
[b] Capecitabine versus 5-FU/LV; Non-inferiority margin of 1.20 corresponds to the retention by XELODA of approx. 75% of the 5-FU/LV effect on DFS
[c] Wald chi square test for differences of XELODA vs 5-FU/LV

**Metastatic Colorectal Cancer**

Data from two multicenter, randomized, controlled phase III clinical trials involving 603 patients and one randomized phase II trial of 34 patients support the use of XELODA in the first-line treatment of patients with metastatic colorectal carcinoma (refer to Table 14).

**Table 14 Clinical Studies in Metastatic Colorectal Carcinoma - Monotherapy**

| **-Design**<br>**-Diagnosis** | **Drug/Dosage** | **No. of Patients Enrolled**<br>**-Demographic Data** | **Results** |
|---|---|---|---|
| **PIVOTAL PHASE III STUDIES**<br><br><u>Study 1:</u><br><br>randomized, controlled, multicenter | -capecitabine 2500 mg/m$^2$/day for 2 weeks with a 1 week rest period (given as 3 week cycles) | N=302<br>Age (yrs) - Md: 64; range: 23 -86<br>M/F: 181(60%)/ 121(40%)<br>Karnofsky PS- Md: 90%; range: 70 - 100<br>Colon /Rectum: 222 (74%)/ 79 (26%)<br>Prior radiation therapy: 52 (17%)<br>Prior adjuvant 5-FU: 84 (28%) | -overall response rate:<br>capecitabine - 21%<br>5-FU/LV - 11%<br>(p=0.0014)<br><br>-median time to progression:<br>capecitabine - 128 days<br>5-FU/LV - 131 days<br>(p=0.90) |
| | -5-FU/leucovorin (LV) Mayo regimen* | N=303<br>Age (yrs) - Md: 63; range: 24 - 87<br>M/F: 197(65%)/ 106(35%)<br>Karnofsky PS- Md: 90%; range: 70 - 100<br>Colon /Rectum: 232 (77%)/ 70 (23%)<br>Prior radiation therapy: 62 (21%)<br>Prior adjuvant 5-FU: 110 (36%) | -median survival:<br>capecitabine - 380 days<br>5-FU/LV - 407days<br>(p=0.24) |

| -Design<br>-Diagnosis | Drug/Dosage | No. of Patients Enrolled<br>-Demographic Data | Results |
|---|---|---|---|
| <u>Study 2:</u><br><br>randomized, controlled, multicenter | -capecitabine 2500 mg/m$^2$/day for 2 weeks with a 1 week rest period (given as 3 week cycles) | N=301<br>Age (yrs) - Md: 64; range: 29 - 84<br>M/F: 172(57%)/ 129(43%)<br>Karnofsky PS- Md: 90%; range: 70 - 100<br>Colon /Rectum: 199 (66%)/ 101 (34%)<br>Prior radiation therapy: 42 (14%)<br>Prior adjuvant 5-FU: 56 (19%) | -overall response rate:<br>capecitabine - 21%<br>5-FU/LV - 14%<br>(p=0.027)<br><br>-median time to progression:<br>capecitabine - 137 days<br>5-FU/LV - 131 days<br>(p=0.68) |
| | -5-FU/leucovorin (LV) Mayo regimen* | N=301<br>Age (yrs) - Md: 64; range: 36 - 86<br>M/F: 173(57%)/ 128(43%)<br>Karnofsky PS- Md: 90%; range: 70 - 100<br>Colon /Rectum: 196 (65%)/ 105 (35%)<br>Prior radiation therapy: 42 (14%)<br>Prior adjuvant 5-FU: 41 (14%) | -median survival:<br>capecitabine - 404 days<br>5-FU/LV - 379 days<br>(p=0.30) |
| **PHASE II STUDY**<br>randomized, open label | -capecitabine 1331 mg/m$^2$/day (continuous)<br>-capecitabine 2510 mg/m$^2$/day (intermittent)<br>-capecitabine 1657 mg/m$^2$/day/ leucovorin 60 mg/day (intermittent) | 39<br>34<br>35<br>Patients with advanced and/or metastatic colorectal carcinoma | -objective response rate:<br>22%<br>25%<br>24% |

*20 mg/m$^2$ leucovorin I.V. followed by 425 mg/m$^2$ I.V. bolus 5-FU on days 1 to 5, every 28 days.

XELODA was superior to 5-FU/LV for objective response rate in Study 1 and Study 2. The response rate observed in patients receiving the Mayo regimen was consistent with the published literature. It was also observed that in patients who received prior adjuvant chemotherapy the objective response rate was 15.3% and 14.5% for capecitabine and 5.5% and 4.4% (Study 1 and 2, respectively) for 5-FU/LV. There was no difference in time to disease progression and survival as compared to 5-FU/LV for both studies.

**Combination therapy – Second-line treatment of metastatic colorectal cancer**

Data from a multicenter, randomized, controlled phase III clinical study (NO16967) support the use of XELODA in combination with oxaliplatin for the second-line treatment of metastastic colorectal cancer. In this trial, 627 patients with metastatic colorectal carcinoma who have received prior treatment with irinotecan in combination with a fluoropyrimidine regimen as first-line therapy were randomized to treatment with XELOX or FOLFOX-4. For the dosing schedule of XELOX and FOLFOX-4, refer to Table 15 below.

**Table 15 Treatment Regimens in Study NO16967**

| | Treatment | Starting Dose | Schedule |
|---|---|---|---|
| FOLFOX-4 | Oxaliplatin | 85 mg/m$^2$ IV 2 h | Oxaliplatin on Day 1, every 2 weeks |
| | Leucovorin | 200 mg/m$^2$ IV 2 h | Leucovorin on Day 1 and 2, every 2 weeks |
| | 5-Fluorouracil | 400 mg/m$^2$ IV bolus, 600 mg/ m$^2$ IV 22 h | 5-fluorouracil IV bolus/infusion, each on Days 1 and 2 , every 2 weeks |
| XELOX | Oxaliplatin<br>Capecitabine | 130 mg/m$^2$ IV 2 h<br>1000 mg/m$^2$ oral bid | Oxaliplatin on Day 1, every 3 weeks<br>Capecitabine oral bid for 2 weeks (followed by 1 week off treatment) |

5-Fluorouracil: IV bolus injection immediately after leucovorin

XELOX is at least equivalent to FOLFOX-4 in terms of progression-free survival in the per protocol population and intent-to-treat population in the investigator assessments. Progression-free survival by the IRC assessment also met the NI margin of 1.23 (HR = 0.93; 95% CI [0.74; 1.17]). Exploratory subgroup analyses for PFS (EP population) and OS (ITT population) for age suggest that XELOX may be less effective than FOLFOX-4 in patients ≥ 65 years of age (HR 1.32, 95% CI, 0.98-1.78 and HR 1.34, 95% CI, 1.00-1.80, respectively).

No quality of life data was collected. The median follow up at the time of the primary analyses in the intent-to-treat population was 2.1 years; data from analyses following an additional 6 months of follow up are also included in the table below.

**Table 16 Key Non-Inferiority Efficacy Results for the Primary Analysis and 6-month Follow-up Data (PPP and ITT Populations, Study NO16967)**

| PRIMARY ANALYSIS<br>PFS by Investigator Assessment* | | | | | |
|---|---|---|---|---|---|
| | XELOX | | FOLFOX-4 | | |
| Population | # events | Median Time to Event (Days) | # events | Median Time to Event (Days) | HR (97.5% CI) |
| PPP | 244 | 154 | 247 | 168 | 1.03 (0.87; 1.24) |
| ITT | 301 | 144 | 301 | 146 | 0.97 (0.83; 1.14) |
| OS<br>ADDITIONAL 6-MONTHS OF FOLLOW UP | | | | | |
| ITT | 270 | 363 | 270 | 382 | 1.02 (0.86; 1.21) |

*PFS by IRC assessment (PPP) met the NI margin of 1.23 (HR = 0.93; 95% CI [0.74; 1.17])

**Breast Carcinoma:**
XELODA has been evaluated in breast cancer clinical trials in combination with docetaxel and as monotherapy. Table 17 summarizes data from a pivotal combination trial as well as from one pivotal and two supportive monotherapy phase II clinical trials.

**XELODA in Combination with Docetaxel:** The dose of XELODA used in combination with docetaxel in the phase III clinical trial was based on the results of a phase I study, where a range of doses of docetaxel given every 3 weeks in combination with an intermittent regimen of XELODA were evaluated. The combination dose regimen was selected based on the tolerability profile of the 75 mg/m$^2$ every 3 weeks of docetaxel in combination with 1250 mg/m$^2$ twice daily for 14 days of XELODA administered every 3 weeks. The approved dose of 100 mg/m$^2$ of docetaxel administered every 3 weeks was the control arm of the phase III study.

As shown in Table 17, 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.

Health Related Quality of Life (HRQoL) was assessed using EORTC QLQ-C30 (version 2) and Breast Cancer Module of the EORTC (BR23). HRQoL was similar in the two treatment groups. Approximately 11% of patients in the combination arm and 10% in the monotherapy arm did not complete a quality of life questionnaire at least once either at baseline or during the treatment phase.

## Table 17 Clinical Studies in Breast Carcinoma

| -Design<br>-Diagnosis | Drug/Dosage | No. Women Enrolled | Results |
|---|---|---|---|
| | | | |
| | ~~222~~ | | |
| **PIVOTAL STUDY - MONOTHERAPY** | | | |
| -open label<br>-females with advanced or metastatic breast cancer refractory to previous paclitaxel therapy: (77% resistant, 23% failed paclitaxel; 41% resistant, 26% failed anthracycline therapy; 82% prior 5-FU exposure). | -capecitabine 2510 mg/m$^2$/day for 2 weeks with a 1 week rest period (given as 3 week cycles) | 162 (135 measurable disease) | -overall response rate (ORR) intent-to-treat (n=135): 20% (95% CI:13.6-27.8); 3 complete responses<br>-ORR (standard population, n=117): 23% (min. 6 weeks therapy)<br>-median duration of response: 241 days<br>-median time to progression: 93 days<br>-median survival: 384 days<br>-clinical benefit response: positive 29 pts. (20%); stable 45 pts. (31%). In 51 pts. with baseline pain ≥20 mm (visual analogue scale), 24 pts. (47%) positive response in pain intensity (≥50% decrease) |
| **SUPPORTIVE STUDIES - MONOTHERAPY** | | | |
| -open label, randomized, parallel group<br>-females ≥55 with advanced or metastatic breast cancer without previous chemotherapy (other than adjuvant treatment) | -capecitabine 2510 mg/m$^2$/day for 2 weeks with a 1 week rest period (given as 3 week cycles)<br>-Cytoxan, methotrexate, 5FU (CMF) 600/40/600 mg/m$^2$ iv q3 weeks. | 95 | -capecitabine response rate: 25% (95%CI: 14%-37%)<br>-CMF response rate: 16% (95% CI: 5%-33%)<br>-median time to disease progression: capecitabine-132 days; CMF-94 days |
| -open-label, randomized parallel group<br>-females with disease progression within 12 months of previous anthracycline treatment | -capecitabine 1331 mg/m$^2$/day (continuous) for 6 weeks<br>-capecitabine 2510 mg/m$^2$/day for 2 weeks with a 1 week rest period (given as 3 week cycles) (intermittent)<br>-paclitaxel 175 mg/m$^2$/q 3weeks | 44 | -capecitabine response rate (intermittent arm): 36% (95%CI: 17-59%); 3 complete responses<br>-paclitaxel response rate: 21% (95% CI: 6-46%).<br>-median time to disease progression: capecitabine 92 days; paclitaxel 95 days. |

| -Design<br>-Diagnosis | Drug/Dosage | No. Women Enrolled | Results |
|---|---|---|---|
| **PIVOTAL STUDY – COMBINATION THERAPY** | | | |
| -open label, randomized, parallel group<br>-females with advanced and/or metastatic breast cancer resistant to or recurring during or after anthracycline-containing therapy or relapsing during or recurring within 2 years of completing anthracycline-containing adjuvant therapy | -capecitabine 2500 mg/m$^2$/day for 2 weeks with a 1 week rest period in combination with docetaxel 75 mg/m$^2$ every 3 weeks<br><br>-docetaxel 100 mg/m$^2$ every 3 weeks | 255<br><br>256 | <u>Response Rate</u><br>Combination therapy: 41.6%<br>Docetaxel monotherapy: 29.7%<br>(p=0.0058)<br><u>Time to Disease Progression</u><br>Combination therapy: 186 days<br>Docetaxel monotherapy: 128 days<br>(p=0.0001)<br>Hazard Ratio: 0.643<br><u>Overall Survival</u><br>Combination therapy: 442 days<br>Docetaxel monotherapy: 352 days<br>(p= 0.0126)<br>Hazard Ratio: 0.775 |

## DETAILED PHARMACOLOGY

### Animal Pharmacology:

Capecitabine administration of doses up to 300 mg/kg (p.o.) in mice and rats and up to 30 mg/kg (i.v.) in anesthetized dogs, produced no biologically significant pharmacodynamic effects on the mammalian nervous, cardiovascular, respiratory, and gastrointestinal systems. At the highest doses [1,000 mg/kg (p.o.) in mice and rats and 100 mg/kg (i.v.) in dogs], capecitabine caused minimal changes in some of the above parameters. In anaesthetized cynomolgus monkeys, capecitabine infused i.v. at 10 and 30 mg/kg did not affect the parameters relating to cardiovascular and respiratory function. At 100 mg/kg (i.v.), it caused slight and transient hypotension and suppressed cardiac function. These effects were not considered critical.

**Metabolic Conversion of Capecitabine in Animals:** The cynomolgus monkey is the most predictive model of the toxicity that may occur in humans as the activity and distribution of the metabolizing enzymes carboxylesterase and cytidine deaminase are similar in this species to those seen in humans. In the mouse, as in humans and monkeys, conversion of the parent drug occurs via 5'-DFCR to 5'-DFUR. However, the efficiency of this conversion is less than that of the monkey. In contrast to monkey and mouse, the rat has minimal cytidine deaminase activity in major organs. Therefore, in the latter species, capecitabine is metabolized to 5'-DFCR; however, its subsequent conversion to 5'-DFUR is poor. The low activity of cytidine deaminase in the rat, which results in high plasma levels of 5'-DFCR relative to monkey and man, allowed the toxicity of 5'-DFCR to be investigated. For these reasons, the teratology and reproductive toxicity studies were conducted in the mouse and the monkey.

**Mechanism of Action:** 5-FU is further metabolized to 5-fluoro-2'-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP) and causes cell injury by two primary mechanisms. First, FdUMP binds covalently to thymidylate synthase (TS) and prevents

formation of thymidylate, the precursor of thymidine triphosphate that is required for DNA synthesis, thereby inhibiting cell proliferation. The second mechanism results from the incorporation of FUTP into RNA in place of UTP, thereby preventing the correct nuclear processing of ribosomal RNA and messenger RNA. These effects are most marked on rapidly proliferating cells, such as tumour cells, which utilize 5-FU at a higher rate.

**Clinical Pharmacokinetics:**

The pharmacokinetics of capecitabine and its metabolites have been evaluated in 11 studies in a total of 213 cancer patients at a dosage range of 502 to 3514 mg/m2/day. The parameters of capecitabine, 5'DFCR and 5'DFUR measured on days 1 and 14 were similar. AUC of 5-FU was 30% higher on day 14, but did not increase subsequently (day 22). At therapeutic doses, the pharmacokinetics of capecitabine and its metabolites were dose proportional, except for 5-FU. The elimination half-life of both capecitabine and 5-FU were about 45 minutes.

**Absorption:** The gastrointestinal absorption of capecitabine and its metabolites (5'-DFCR, 5'-DFUR and 5-FU) was rapid (median 2 hours; range 0.5 to 5 hours). Capecitabine is extensively absorbed since at least 70% of the dose was recovered in urine with low variability (CV of 30%).

**Distribution:** Binding of $^{14}$C-capecitabine, $^{14}$C-5'-DFCR and $^{3}$H-5'-DFUR to human plasma proteins were determined *in vitro* by ultrafiltration. The concentration ranges used (0.2/0.5 to 200/500 µgmL) encompassed the concentrations observed in plasma species *in vivo*. Plasma protein binding of capecitabine is low (54%, 10% and 60% for capecitabine, 5'-DFCR and 5'-DFUR, respectively) and is not concentration-dependent. Capecitabine was primarily bound to human albumin (approximately 35%).

**Excretion:** In three studies, concentrations of capecitabine and its metabolites (5'-DFCR, 5'-DFUR, 5-FU, FUH2, FUPA and FBAL) were measured in urine. Over 70% of the capecitabine dose was recovered in urine as drug-related material. The majority of the dose was recovered as FBAL (approximately 50%).

## TOXICOLOGY

The tables presented on the following pages provide the findings of the main toxicology, mutagenicity/genotoxicity and reproduction/teratology studies performed with capecitabine:

**Acute Toxicity**:

| Title | Species/ Strain | No./Sex/ Dose | Dose (mg/kg) | Duration of Observations/ Route of Administration | Maximum Non-Lethal Dose | Target Organs/Systems of Toxicity |
|---|---|---|---|---|---|---|
| Mouse Acute Study | Mouse / BDF1 | 5 | 250, 375, 500 | 14 days Intravenous | > 250 - < 375 mg/kg for males<br>> 375 - < 500 mg/kg for females | High-Dose: 3 males and 2 females died. Transient ↓ spontaneous motor activity immediately after to 1 hour after dosing.<br>Mid-Dose: One male died. Transient ↓ spontaneous motor activity immediately after to 1 hour after dosing.<br>Low-Dose: No adverse effects observed. |
| Mouse Acute Study | Mouse / BDF1 | 5 | 1000, 2000 | 14 days Oral (gavage) | > 2000 mg/kg (limit dose) | Low & High Doses: Transient ↓ spontaneous motor activity from 15 minutes after dosing to 1 hour at 1000 mg/kg and 2-4 hours at 2000 mg/kg (↓ respiratory rate & prostration at high dose only). Transient ↓ food consumption, males, on day of dosing. |
| Rat Acute Study | Rat / (SD-Slc) | 5 | 1000, 2000 | 14 days Oral (gavage) | > 2000 mg/kg (limit dose) | Low Dose: ↓ spontaneous motor activity and muscle relaxation (1 female) from 15-30 minutes after dosing.<br>High Dose: ↓ spontaneous motor activity, muscle relaxation, and immobility in males and females, and slight salivation in 1 female from 15 minutes-4 hours after dosing |
| Monkey Pyramiding Study | Monkeys / Cynomolgus | 2 males only | 500, 1000, 2000[1] | 14 days after final dosing Oral (naso-gastric) | > 2000 mg/kg (limit dose) | Low Dose: Emesis within 15 minutes of dosing; loose feces/diarrhea in 1 monkey the day after dosing.<br>Mid-Dose: Emesis 1.5 or 6 hours post-dosing; loose feces/diarrhea in 1 monkey 6 hours after dosing.<br>High Dose: Emesis within 15 minutes of dosing; salivation immediately after dosing; loose feces/diarrhea for approximately 1 week after dosing. |

[1] 500 mg/kg (day 1), 1000 mg/kg (day 4), 2000 mg/kg (day 7)

## Subchronic and Chronic (Long-Term) Toxicology Studies:

| Title | Species/Strain | No./ Sex/ Dose | Dose (mg/kg/ day) | Duration / Route of Adminis-tration | Target Organs / Systems of Toxicity |
|---|---|---|---|---|---|
| 4-Week Mouse Study | Mouse / BDF1 | 6 | 0<br>198<br>395<br>791 | 4 weeks<br>Oral<br>(gavage) | Mid & High Doses: Slight anemia,↑BUN (slight); ↑spleen weight (slight); enlarged nuclei and degenerated crypt cells in small intestine, ↑extramedullary hematopoiesis in spleen<br><br>High Dose: ↓BMC (slight); ↓thymus weight (slight); slight atrophic changes in thymus and spleen, degeneration of hematopoietic cells in bone marrow |
| 13-Week Mouse Study | Mouse / BDF1 | 151[1] | 0<br>198<br>395<br>791/593[2] | 13 Weeks + 4 weeks Recovery<br>Oral<br>(gavage) | Mid & High Dose: ↓RBC, ↑MCV, MCH, PLT; ↑spleen weight, ↓ovary weight; splenic extramedullary hematopoiesis, increased ratio of neutrophil myelocytes & degenerated erythroblasts in bone marrow, changes in female reproductive organs, regressive change of gastrointestinal tract<br>High Dose: Mortality (11/30); ↓body weight, food intake; emaciation, ↓spontaneous motor activity, loose feces; ↓HCT, Hb, BMC; ↓testis & epididymis weights; atrophy of lymph node nodules and of thymus, ↓erythroblasts in bone marrow, changes in male reproductive organs. Found dead & moribund sacrificed mice also showed hyposthenia, hypothermia, bradypnea, or convulsion; ↓WBC, ↑reticulocytes; ↓thymus & uterus weights, ↑relative adrenal weight; atrophy of epidermis/sebaceous glands/hair follicles in skin.<br>Recovery High Dose: ↑PLT, reticulocyte, BMC; enlarged spleen with increased weight; extramedullary hematopoiesis in spleen, ↑neutrophil myelocytes in bone marrow |
| 4-Week Rat Study | Rat / (SD-Slc) | 5 | 0<br>179.5<br>359<br>538.5 | 4 Weeks<br>Oral<br>(gavage) | High Dose: Slight ↓body weight gain and food intake (males); slight degeneration of rectal crypt cells |
| 26-Week Rat Study | Rat / (SD-Slc) | 20 | 0<br>179.5<br>359<br>538.5 | 26 Weeks<br>Oral<br>(gavage) | High and Mid Doses: ↓Body weight gain and food intake (males); ↑MCH, MCV (very slight), ↓serum total protein (very slight/males); proteinuria<br>High Dose: (males only) ↓RBC (very slight); ↓urine volume and ↑specific gravity (slight); slight histopathologic changes in rectum (degenerated crypt cells, dilatation of glandular lumina, enlarged nuclei of crypt cells or epithelium) |

[1] 10 for 13 week dosing, 5 for recovery.
[2] The high dose was changed from 791 mg/kg/day to 593 mg/kg/day on day 37.

| Title | Species/ Strain | No./ Sex/ Dose | Dose (mg/kg/ day) | Duration / Route of Adminis-tration | Target Organs / Systems of Toxicity |
|---|---|---|---|---|---|
| 4-Week Monkey Study & Toxico-kinetics | Monkey/ Cynomolgus *(Macaca fascicularis)* | 3 (High dose: males only) | 0<br>35.9<br>179.5<br>359 | 4 Weeks Oral (gavage) | Mid Dose: Decrease in duodenal and ileal mucosal folds<br>Mid & High Doses: Loose feces, diarrhea; ↓body weight & food intake; ↓WBC, BMC; ↓thymus weight; gastrointestinal changes (dilated glandular lumina, enlarged nuclei of epithelial cells and crypt cells, atrophic glands), atrophic acinar cells in pancreas, atrophic lymph follicles in lymph nodes, spleen and tonsils, atrophic thymus, hypoplasia of hematopoietic cells in bone marrow, atrophy of acinar cells in salivary glands<br>High Dose: Mortality - 2 males sacrificed moribund; emesis; in addition, 2 males sacrificed moribund showed ↓spontaneous motor activity, emaciation, hypothermia, lying on the side, staggering gait; atrophic mucosa and glands, enlarged glandular lumina, enlarged nuclei of mucosal epithelial cells and crypt cells in stomach and small intestine, atrophy of mucosal epithelium of tongue and esophagus, degeneration and hypertrophy of cortical cells, and hemorrhage in cortex of adrenals |
| 13-week Monkey Study & Toxico-kinetics | Monkey / Cynomolgus (*Macaca fascicularis*) | 4 | 0<br>54<br>108<br>215/162 [1] | 13 Weeks + 4 Weeks Recovery Oral (gavage) | Mid & High Doses: Loose feces; ↓RBC, WBC, HCT, Hb; small thymus and spleen, atrophied splenic nodules, decrease of lymphocyte in thymic cortex.<br>High Dose: Mortality - 1 male died, 1 female sacrificed moribund; ↓food intake; ↓thymus & spleen weights; atrophied lymph nodules in tonsil.<br>In addition, monkeys that died or were sacrificed moribund showed poor appetite, diarrhea, staggering gait, emesis, lying on the belly, ↓spontaneous motor activity, emaciation, hypothermia, pale oral mucosa; ↓body weight; ↓BMC, ↑platelet; enlarged adrenal & ↑weight; ↓adipose tissue, atrophy of thymus, regressive degeneration of gastrointestinal tract, lymphatic, & hematopoietic organs.<br>No findings after recovery period. |

[1] Days 0-31:215 mg/kg/day; days 32-34: cessation of administration; days 35-90: 162 mg/kg/day

| Title | Species/ Strain | No./ Sex/ Dose | Dose (mg/kg/ day) | Duration / Route of Administration | Target Organs / Systems of Toxicity |
|---|---|---|---|---|---|
| 26-Week Monkey Study | Monkey / Cynomolgus (*Macaca fascicularis*) | 3 | 0<br>18<br>54<br>144 | 26 Weeks<br>Oral<br>(gavage) | High Dose: Mortality (1 female sacrificed moribund); loose feces; ↓WBC (segmented neutrophils, lymphocytes), RBC, HCT and Hb; atrophy of thymus & lymphoid follicle of spleen.<br>In addition, female monkey sacrificed moribund showed diarrhea, ↓spontaneous motor activity, loss of appetite, pale oral mucosa, emaciation, prone position, hypothermia, bradypnea; ↓body weight & food intake; ↓BMC, ↑relative lymphocytes, ↓total cholesterol, glucose, Ca, Na, K, Cl, ↑creatinine, BUN, α-1 globulin; enlarged adrenals, small thymus, liquid feces in large intestine, no contents in stomach or small intestine; ↓absolute weights of heart, liver, kidney, thymus, ↑relative weights of brain, lung, adrenals; histopathologic changes in digestive system (degeneration or hyperplasia of mucosal epithelium, hyperplasia of muscularis mucosa, fibroplasia of submucosa, blunting and fusing of villi); atrophy of lymphoid follicles of spleen; atrophic thymus; lymphocyte depletion of mesenteric lymph node; decreased cellularity of bone marrow; hypoplasia of squamous epithelium in skin, mammary gland, tongue, esophagus, vagina; atrophy of hair follicle of skin; degranulation of acinar cell in pancreas (islet cells of the pancreas were unaffected). |
| 52-Week Monkey Study & Toxico-kinetics | Monkey / Cynomolgus (*Macaca fascicularis*) | 4 | 0<br>36<br>72<br>108 | 52 weeks<br>Oral<br>(gavage) | All treated groups: Dose-related increase of post-dosing salivation, slight ↓WBC, dosage-related ↑myeloid left shift.<br>High Dose: Regurgitation, ↓relative thymus weight (marginal) with ↓lymphocytes in thymic cortex and proliferated hematopoietic cells in bone marrow. |

**Carcinogenicity Study:**

| Title | Species/Strain | No./ Sex/ Dose | Dose (mg/kg/ day) | Duration / Route of Administration | Target Organs / Systems of Toxicity |
|---|---|---|---|---|---|
| 24-Month Mouse Carcino-genicity Study | Mouse / BDF1 | 50/ sex/ group | 0 - Control -1<br>0 - Control - 2<br>30, 60, 90 | 24-Month<br>Oral (dietary admixture) | Low Dose: ↑ MCV, MCH (females only)<br>Mid Dose: ↑ MCV, MCH, ↓ RBC, ↓ testes weights<br>High Dose: ↓RBC, Hb, HCT, ↑ MCV, MCH, platelets<br>↓ Thymus and testes weight (males only)<br>There was no evidence of an oncogenic potential |

**Mutagenicity and Genotoxicity Studies**:

| Title | Assay System | Concentration of Capecitabine Assayed | Duration of Exposure | Genotoxic and Other Findings |
|---|---|---|---|---|
| Bacterial Cell Gene Mutation (Exploratory) | Ames Test: standard plate incorporation method using strains TA98 & TA100 of *Salmonella typhimurium* with & without metabolic activation (S9 mix) | 4 to 1000 µg/plate | 48 hrs | No mutagenic activity observed with or without metabolic activation. |
| Gene mutation test in Cultured Mammalian Cells | Chinese hamster lung cells V79/HPRT with and without metabolic activation | 100 to 4000 µg/mL (without metabolic activation)<br>100 to 5000 µg/mL (with metabolic activation) | 16 hrs (without metabolic activation)<br>5 hrs (with metabolic activation) | No mutagenic activity observed with or without metabolic activation.<br>Cytotoxicity<br>Relative cell viability:<br>42-51% at 4000 µg/mL without metabolic activation<br>50-92% at 5000 µg/mL with metabolic activation |
| Chromosome Aberration *(in vitro)* | Human peripheral blood lymphocytes with and without metabolic activation | 50 to 500 µg/mL (without metabolic activation)<br>250 to 3600 µg/mL (with metabolic activation) | 24 & 48 hrs (without metabolic activation)<br>3 hrs (with metabolic activation) | Without metabolic activation:<br>Clastogenic and cytotoxic at doses of 250 & 500 µg/mL.<br>With metabolic activation:<br>Not clastogenic or cytotoxic. |
| Chromosome Aberration *(in vivo)* | Mouse micronucleus test<br>Strain: Füllinsdorf Moro Albino | Oral Dose (mg/kg)<br>500<br>1000<br>2000 | Post-dose<br>24 hrs<br>24 hrs<br>24 & 48 hrs | The frequency of micronucleated polychromatic erythrocytes was not statistically significantly increased at any of the sampling times. No signs of toxicity in bone marrow cells. |

**Reproduction and Teratology Studies**:

| Title | Species/ Strain | No./Sex/ Dose | Dose (mg/kg/ day) | Duration /Route of Administration | Target Organs / Systems of Toxicity |
|---|---|---|---|---|---|
| Mouse Fertility Study | Mouse / BDF1 | 24 | 0<br>190<br>380<br>760 | Males: 28 days before, through confirmation of fertility<br>Females: 14 days before, through mating & until day 6 of gestation<br><br>Oral<br>(gavage)<br><br>Recovery: following cessation of treatment, high-dose females that had unsuccessfully mated were re-mated with control or high-dose males. | **Parental mice:** No drug-related deaths.<br>High Dose: ↓body weight gain & food intake, emaciation, slight ↓spontaneous motor activity; ↓mating index (due to disturbed estrous cycle) & female fertility index; ↓testes & epididymes weights, degeneration & decrease of spermatocytes & spermatids in testes, ↑degenerative spermatogenic cells in epididymes in males; no live fetuses, ↑resorptions (early deaths).<br>Mid Dose: ↓live fetuses, ↑resorptions (early deaths).<br>**Fetus:**<br>Slight ↓female fetal body weights, slight ↑fetuses with external anomalies.<br>**Recovery:**<br>Adverse effects reversed. No adverse effects on reproductive performance, fetal viability, or body weight; no fetal malformations. |
| Mouse Embryo-toxicity & Terato-genicity Study | Mouse / BDF1 | ca. 20 mated females | 0<br>190<br>395<br>791 | Day 6 - 15 of gestation<br>(1st day of gestation = day 0)<br><br>Oral<br>(gavage) | **Dams:** No drug-related deaths.<br>All treated groups: Dose-dependent ↓body weight gain & food intake; dose-dependent ↓live fetuses and ↑early resorption rate.<br>High Dose: No live fetuses.<br>High & Mid Doses: Most had complete resorptions.<br>Mid Dose: Only one dam with live fetuses.<br>Low Dose: Slight ↑late resorptions.<br>**Fetus:**<br>Mid Dose: Oligodactyly.<br>Mid and Low Dose: ↓fetal body weight.<br>Low Dose: Cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail; dilated cerebral ventricles. |

| Title | Species/ | No./Sex/ | Dose | Duration /Route of | Target Organs / Systems of Toxicity |
|---|---|---|---|---|---|

| | Strain | Dose | (mg/kg/ day) | Administration | |
|---|---|---|---|---|---|
| Mouse Embryo-toxicity & Teratogenicity Study (Supplement to Study Ref. 2302) | Mouse/ BDF1 | ca. 20 mated females | 0<br>25<br>50<br>100 | Day 6 - 15 of gestation<br>(1st day of gestation = day 0)<br>Oral (gavage) | **Dams:**<br>All groups: No drug-related deaths.<br>High Dose: Slight ↓body weight gain and food intake.<br>**Fetus:** No treatment-related effects. |
| Mouse Embryo-toxicity & Teratogenicity Study (Supplementary Segment II - F1 pup evaluation) | Mouse/ BDF1 | ca. 20 mated females | 0<br>50<br>100<br>200 | Day 6 - 15 of gestation<br>(1st day of gestation = day 0)<br>Oral (gavage) | **Dams:** No drug-related deaths.<br>High Dose: Slight ↓body weight gain and food intake; slightly prolonged gestation period.<br>**Pups:**<br>High Dose: ↓Live neonates, ↓viability index from day 0 to day 4 after birth, slight ↓body weight gain, ↑number of pups with skeletal abnormalities (domed head, kinky tail), retardation of ossification, slight ↑ambulation in open field test.<br>High & Mid Doses: Deaths with domed head and hydrocephaly; swollen spleen at necropsy with extramedullary hematopoiesis. |
| Monkey<br>Preliminary Embryo-toxicity & Terato-genicity Study | Monkey / Cynomolgus (*Macaca fascicularis*) | 2 pregnant females | 90<br>180 | Day 20 - 50 of gestation<br>Oral (gavage) | **Dams:** No deaths in any group.<br>High Dose: Abortion (1 between days 40 - 50 of gestation).<br>High and Low Doses: Embryonic death (1 in each group, high dose on day 40 of gestation, low dose on day 50 of gestation); ↓food intake in dams with embryonic death and abortion.<br>**Fetus:**<br>High and Low Doses: No placental or external anomalies in dead embryos or live fetuses.<br>Low Dose:<br>One normal male fetus; no abnormalities in body weight, or visceral or skeletal findings. |

| Title | Species/ Strain | No./Sex/ Dose | Dose (mg/kg/ day) | Duration /Route of Administration | Target Organs / Systems of Toxicity |
|---|---|---|---|---|---|
| Monkey<br>Embryo-toxicity<br>& Terato-genicity Study | Monkey / Cynomolgus (*Macaca fascicularis*) | 5<br>pregnant females | 0<br>22.5<br>45<br>90 | Day 20 - 50 of gestation<br><br>Oral (gavage) | **Dams**<br>No maternal deaths or adverse effects.<br>High Dose: Abortion (1 between days 30 - 40 of gestation).<br>Low Dose: Embryonic death (1 on day 30 of gestation).<br><br>**Fetus:**<br>No treatment-related changes observed in the examinations of live fetuses. |
| Mouse<br>Peri- and Post-natal Study<br>(Segment III) | Mouse/ BDF1 | ca. 20 mated females (F0 generation) | 0<br>100<br>200<br>400 | From day 15 of gestation, through lactation to day 20 post-partum<br>(First day of gestation = gestation day 0)<br>(First day of lactation = lactation day 0)<br><br>Oral (gavage) | **Dams:**<br>No treatment-related deaths or adverse effects.<br><br>**Pups (F1):**<br>No treatment-related findings. |

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**PART III: CONSUMER INFORMATION**

**PrXELODA®**
capecitabine tablets

**This leaflet is part III of a three-part "Product Monograph" published when XELODA (pronounced zeh-LO-da) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about XELODA. Contact your doctor or pharmacist if you have any questions about the drug.**

## ABOUT THIS MEDICATION

**What the medication is used for:**
XELODA is a prescription medication that is used to treat the following types of cancer:

**Adjuvant therapy, stage III colon cancer**
XELODA is used to treat cancer of the colon following complete surgical removal. The intent of treatment with XELODA is to prevent or delay the recurrence of cancer (cure).

**Advanced or metastatic cancer**
XELODA is used to treat *advanced or metastatic breast cancer*. Metastatic means that the cancer has spread outside the breast. When breast cancer has not responded to other chemotherapy medications, XELODA may be one of the choices considered for treatment. Your doctor may prescribe XELODA either alone or in combination with a chemotherapy drug called Taxotere® (also known as docetaxel).

XELODA is also used to treat *metastatic colorectal cancer* that has spread outside of the colon and/or rectum. XELODA may be one of the choices considered for treatment. Your doctor may prescribe XELODA either alone or in combination with a chemotherapy drug called Eloxatin® (also known as oxaliplatin).

**What it does:**
XELODA belongs to a family of medications called the fluoropyrimidines. These medications interfere with the growth of cells that rapidly divide in the body, including cancer cells. XELODA is an inactive substance on its own. When XELODA is taken, it is changed in the body, mostly within the tumour (cancer cells). It changes to become the commonly used cancer medication called 5-fluorouracil (also known as 5-FU). In some patients 5-FU will kill cancer cells and decrease the size of the tumour.

**When it should not be used:**
- If you are allergic to the medicinal ingredient (capecitabine) or to 5-fluorouracil.
- If you are allergic to any of the other non-medicinal ingredients it contains (see '**What the non-medicinal ingredients are**')
- If you suffer from severe kidney disease
- Your body does not have the enzyme DPD (dihydropyrimidine dehydrogenase).
- If you are being treated now or have been treated in the last 4weeks with brivudine, sorivudine or similar classes of substance[1] as part of herpes zoster (chickenpox or shingles) therapy.

**What the medicinal ingredient is:**
capecitabine

**What the important non-medicinal ingredients are:**
XELODA tablets contain the following non-medicinal ingredients:
croscarmellose sodium, hydroxypropyl methylcellulose, iron oxides (yellow and red), lactose anhydrous, magnesium stearate microcrystalline cellulose, talc, titanium dioxide.

**What dosage forms it comes in:**
XELODA is available as tablets that are taken by mouth. The tablets are coated and oblong shaped.

XELODA tablets come in two strengths:
150 mg tablets are light peach coloured, with XELODA engraved on one side and 150 on the other side. The 150 mg tablets are available in bottles containing 60 tablets or in blister packs containing 60 tablets (10 tablets per blister card and 6 blister cards per carton).

500 mg tablets that are peach coloured with XELODA engraved on one side and 500 on the other side. The 500 mg tablets are available in bottles containing 120 tablets or in blister packs containing 120 tablets (10 tablets per blister card and 12 blister cards per carton).

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

**Serious side effects include:**
- **Severe dehydration may cause rapid loss of kidney functions including kidney failure that may lead to death.**
- **Similar to other cancer medicines of the same class, toxicity that may lead to sudden death due to heart problems including irregular heartbeat.**
- **Severe skin reactions such as hand-and foot syndrome, Stevens-Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN].**
- **Severe toxicity due to 5-FU has been associated with deficiency of dihydropyrimidine dehydrogenase (DPD) activity, an enzyme involved in fluorouracil degradation. Deaths have been reported.**
- **Increased action of other medicines used to thin your blood such as warfarin leading to serious side effects.**

**BEFORE you use XELODA talk to your doctor or pharmacist if:**
- you ever had a bad reaction to capecitabine, 5-FU or any

[1] sorivudine and its chemically related analogues, such as brivudine are not approved in Canada.

of the non-medicinal ingredients.
- you are allergic to other medications, food and dyes.
- you have been told you lack the DPD enzyme.
- you are taking any other medications, including those not prescribed by your doctor.
- you are taking warfarin (Coumadin®). Your doctor may need to check the clotting time of your blood more often.
- you are taking phenytoin (Dilantin®) or fosphenytoin (Cerebyx®). Your doctor may need to check the levels of phenytoin in your blood more often.
- you have any other illnesses or diseases affecting your kidneys, liver, or heart.
- you are pregnant, plan to become pregnant or are breastfeeding.

The safety and effectiveness of XELODA in persons <18 years of age has not been established.

This information will help your doctor and you decide whether you should use XELODA and what extra care may need to be taken while you are on the medication.

**What else should you remember while you are taking XELODA?**
- XELODA may impair fertility in females and males of reproductive potential.
- Female Patients: If you are of childbearing age you should avoid becoming pregnant while taking XELODA and it is recommend to be tested to show that you are not pregnant. No research studies have been done with pregnant women. However, studies with animals suggest that XELODA may cause serious harm to an unborn child. An effective method of contraception should be used during treatment and for 6 months after the last dose of XELODA. If the patient becomes pregnant while receiving XELODA, the potential hazard to the fetus must be explained.
- Male Patients: If you are a male, you are advised not to father a child during treatment. Male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of XELODA.
- You should stop breastfeeding during treatment with XELODA and for 2 weeks after the final dose.
- If you are over 65 years old or have a history of heart disease, you may be more sensitive to XELODA. Watch more carefully for possible unwanted effects.
- If you are over 80 years old, your stomach may be more sensitive to XELODA. Watch more carefully for possible unwanted effects.

**Driving and using machines:** XELODA may make you feel dizzy, nauseous or tired. It is therefore possible that XELODA could affect your ability to drive a car or operate machines.

If you experience persistent or severe hand-and-foot syndrome while taking XELODA, it can eventually lead to loss of fingerprints, which could impact your identification by fingerprint scan.

## INTERACTIONS WITH THIS MEDICATION

**Drugs that may interact with XELODA include:**
- Medicine used to treat seizures (eg. Phenytoin and Fosphenytoin)
- Blood thinner medicine (eg. warfarin and phenprocoumon)
- Medicine used to treat heartburn and acid indigestion (eg.Maalox®)
- Leucovorin, a medicine used to prevent the harmful effects of cancer chemotherapy medication
- Certain medicines used specifically for treating viral infections (eg. sorivudine and brivudine[2])

## PROPER USE OF THIS MEDICATION

**Usual dose:**
Your doctor prescribed XELODA after carefully studying your condition. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours. Do not give your XELODA to anyone else.

The usual dose of XELODA depends on your body surface size. Your doctor will calculate the dose for you.

You may need to take a combination of 150 mg and 500 mg tablets. **To get the right dose it is very important that you identify the tablets correctly each time you take XELODA.** Taking the wrong tablets could result in an overdose (too much medication) or underdose (too little medication).

Swallow the XELODA tablets whole, with water. Take the tablets within 30 minutes after the end of a meal (breakfast and dinner). XELODA tablets should not be crushed or cut. If you cannot swallow XELODA tablets whole, please speak with your doctor, nurse or pharmacist.

Take the tablets twice a day (morning and evening doses) as your doctor prescribed. Do not take more than your prescribed dose, do not take it more often or for a longer time than your doctor ordered.

XELODA is taken in 21 day cycles. This means you take XELODA for 14 days and then stop taking it for 7 days. It is important to have this rest period. Your doctor will decide how many cycles of treatment you will need.

For the treatment of colon cancer following complete surgical removal, XELODA is usually taken for eight 21-day cycles (i.e. for a total of 24 weeks or approximately 6 months).

[2] sorivudine and its chemically related analogues, such as brivudine are not approved in Canada.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**
If you forget a dose of XELODA do not take the missed dose at all. Take your next dose at the usual time and check with your doctor. Do not take a double dose.

## SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Tell your doctor, nurse or pharmacist as soon as possible if you do not feel well while you are taking XELODA.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

| Symptom / effect | | Talk with your doctor or pharmacist | | Stop taking drug and call your doctor or pharmacist |
|---|---|---|---|---|
| | | Only if severe | In all cases | |
| **Very Common** | diarrhea<br><br>sores in the mouth and throat (called stomatitis)<br><br>tiredness or fatigue<br><br>nausea<br><br>vomiting<br><br>tingling, numbness, pain, swelling, redness or blisters of the palms of the hands or feet (called hand-and-foot syndrome) | | ✓ | |
| **Common** | reduced white blood cells, red blood cells and platelets in the blood<br><br>increased chance of infection<br><br>increased chance of unusual bleeding<br><br>dehydration (increased thirst, dry or sticky mouth) | | ✓ | |
| **Rare** | weakness, lack of energy, shortness of breath, confusion | | ✓ | |
| **Very Rare** | severe skin reactions (redness, pain, swelling or blistering of lips, eyes or mouth, skin peeling and flu-like symptoms.<br><br>weakness of the legs and arms, drowsiness, generalized seizures, headaches, and vision impairment. | | ✓ | |

Stop taking XELODA and call your doctor immediately if you notice any of the following side effects. Your doctor can then adjust XELODA to a dose that is right for you. This should help to reduce the side effects and stop them from getting worse.

**Diarrhea**
- an additional 4 bowel movements a day beyond what is normal or any diarrhea at night
- if you have a colostomy, an increase in loose, watery fluid in your colostomy bag
- any diarrhea in conjunction with soreness of the mouth affecting your ability to drink enough fluids

**Vomiting**
- vomiting more than once in 24 hours, especially if in association with diarrhea

**Nausea**
- loss of appetite or eating less food than usual each day

**Stomatitis**
- painful sores, redness or swelling in the mouth or throat

**Hand-and-foot Syndrome**
- pain, redness, swelling, ulcers or blisters on the hands and feet

**Infection**
- fever; a temperature of 38.0 °C or higher
- signs of infection such as sore throat, cough, or pain when you pass urine

**Heart problems**
- chest pains, abnormal heart rate, edema of extremities

Your doctor may tell you to decrease the dose or stop XELODA treatment for a while. If caught early, most of these side effects usually improve after you stop taking XELODA. If they do not improve within 2 to 3 days, call your doctor again. After side effects have improved, your doctor will tell you whether to start taking XELODA again and what is the right dose for you.

These unwanted effects may differ when taking XELODA in combination with Taxotere® (docetaxel). For example, in addition to the unwanted effects mentioned above which may occur with XELODA alone, the following unwanted effects may occur when XELODA is taken in combination with Taxotere®: hair loss, weakness, fluid retention, nail changes and peripheral neuropathy (numbness, tingling, and burning of the hands and feet), constipation, abdominal pain, indigestion, dry mouth, rash, weakness, pain, taste disturbance, headache, dizziness, inability to sleep, loss or decreased appetite, dehydration, back pain. Please consult your doctor for more information on the possible unwanted effects that may occur when taking XELODA in combination with Taxotere® (docetaxel).

If you are concerned about these or any other unexpected effects while taking XELODA, talk with your doctor, nurse or pharmacist.

***This is not a complete list of side effects. For any unexpected effects while taking XELODA, contact your doctor or pharmacist.***

## HOW TO STORE IT

Keep out of reach and sight of children.

Store at room temperature (15-30°C), in the original labelled container or package.

Special handling using appropriate equipment and disposal procedures, should be taken as XELODA is a cytotoxic drug. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

**REPORTING SUSPECTED SIDE EFFECTS**

**You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:**

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- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  **- Fax toll-free to 1-866-678-6789, or**
  **- Mail to: Canada Vigilance Program**
  **Health Canada**
  **Postal Locator 1908C**
  **Ottawa, Ontario**
  **K1A 0K9**

  **Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.**

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.rochecanada.com or by contacting the sponsor, Hoffmann-La Roche Limited, at: 1-800-762-4388.

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Roche Hoffmann-La Roche Limited
Mississauga, ON L5N 5M8