Xeloda®

Capecitabine

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Cytostatic agent.
ATC Code: L01BC06.

1.2 Type of Dosage Form

Film-coated tablets 500 mg.

1.3 Route of Administration

Oral.

1.4 Sterile/Radioactive Statement

Not applicable.

1.5 Qualitative and Quantitative Composition

Active ingredient: capecitabine
Excipients: lactose (anhydrous), crosscarmellose sodium, hypromellose, microcrystalline cellulose, magnesium stearat, opadry pink.
The film-coated tablets are biconvex and oblong; they are peach-coloured respectively.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Breast cancer:
Xeloda in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.
Xeloda is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of a taxane and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

Colon, colorectal cancer:
Xeloda is indicated as adjuvant treatment of patients following surgery of stage III (Dukes Stage C) colon cancer.
Xeloda is indicated as first-line treatment of patients with metastatic colorectal carcinoma.

Gastric cancer:
Xeloda is indicated for treatment of advanced gastric cancer.

2.2 Dosage and Administration

Standard Dosage
Xeloda should only be prescribed by a qualified physician experienced in the utilization of antineoplastic agents. Xeloda tablets should be swallowed whole with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed. Standard and reduced dose calculations according to body surface area for starting

doses of Xeloda of 1250 mg/m^2 and 1000 mg/m^2 are provided in Table 1 and Table 2, respectively.

Xeloda tablets should not be crushed or cut (see section *2.6.2 Postmarketing Experience*). 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 section *4.2 Special Instructions for Use, Handling and Disposal*).

Recommended posology (see section *3.1 Pharmacodynamic Properties*):
Monotherapy
Colon and colorectal cancer
The recommended monotherapy starting dose of Xeloda in the adjuvant treatment of colon cancer or in the treatment of metastatic colorectal cancer 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 7-day rest period.

Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months, i.e. Xeloda 1250 mg/m^2 administered twice daily for 14 days followed by a 7-day rest period, given as 3-week cycles for a total of 8 cycles (24 weeks).

Breast cancer
Given as a single agent, the recommended dose of Xeloda in the treatment of locally advanced or metastatic breast cancer is 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period.

Combination therapy
Breast cancer
In combination with docetaxel, the recommended starting dose of Xeloda in the treatment of metastatic breast cancer is 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks.
Premedication with an oral corticosteroid such as dexamethasone according to the docetaxel summary of product characteristics should be started prior to docetaxel administration for patients receiving the Xeloda plus docetaxel combination.

Advanced gastric cancer
In combination with a platinum-based compound, the recommended dose of Xeloda for the treatment of advanced gastric cancer is 1000 mg/m^2 administered twice daily for 14 days followed by a 7-day rest period. The first dose of Xeloda should be given on the evening of day 1 and the last dose should be given on the morning of day 15.
Premedication to maintain adequate hydration and antiemesis according to the cisplatin summary of product characteristics should be started prior to cisplatin administration for patients receiving the Xeloda plus cisplatin combination.

Dose calculations
Xeloda dose is calculated according to body surface area.

Table 1 Standard and reduced dose calculations according to body surface area for a starting dose of Xeloda 1250 mg/m^2

	Dose level 1250 mg/m^2 (twice daily)				
	Full dose 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%) 950 mg/m^2	Reduced dose (50%) 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
≥ 2.19	2800	2	5	2150	1450

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

	Dose level 1000 mg/m^2 (twice daily)				
	Full dose 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%) 750 mg/m^2	Reduced dose (50%) 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

Dosage adjustments during treatment

General:

Toxicity due to Xeloda administration may be managed by symptomatic treatment and/or modification of the Xeloda dose (treatment interruption or dose reduction). 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, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption.

Patients taking Xeloda should be informed of the need to interrupt treatment immediately if moderate or worse toxicity occurs. Doses of Xeloda omitted for toxicity are not replaced or restored, instead the patient should resume the planned treatment cycle. The following are the recommended dose modifications for toxicity:

Table 3 Xeloda monotherapy dose reduction schedule (3-weekly cycle or continuous treatment)

Toxicity NCIC Grades*	**During a course of therapy**	**Dose adjustment for next cycle (% of starting dose)**
Grade 1	maintain dose level	maintain dose level
Grade 2		
1st appearance	interrupt until resolved to Grade 0-1	100%
2nd appearance	interrupt until resolved to Grade 0-1	75%
3rd appearance	interrupt until resolved to Grade 0-1	50%
4th appearance	discontinue treatment permanently	Not applicable
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	Not applicable
Grade 4		
1st appearance	discontinue permanently or if physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 0-1	50%
2nd appearance	discontinue permanently	Not applicable
* National Cancer Institute of Canada common toxicity criteria were used except for hand-foot syndrome		

<u>Dose modifications for toxicity when Xeloda is used as a 3-weekly cycle in combination with other agents:</u>

Dose modifications for toxicity when Xeloda is used as a 3-weekly cycle in combination with other agents should be made according to Table 3 above for Xeloda and according to the appropriate summary of product characteristics for the other agent.

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

During a treatment cycle for those toxicities considered by the treating physician not to be related to Xeloda (for example, neurotoxicity or ototoxicity), then Xeloda should be continued and the other agent should be discontinued according to the appropriate Prescribing Information.

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.

Dose modifications for toxicity when Xeloda is used continuously in combination with other agents:
Dose modifications for toxicity when Xeloda is used continuously in combination with other agents should be made according to Table 3 above for Xeloda and according to the appropriate summary of product characteristics for the other agent(s).

Haematology:
Xeloda treatment may continue throughout a Grade 3 neutropenic episode. However, the patient should be closely monitored and administration of Xeloda should be interrupted if any Grade 2 clinical event (e.g. diarrhoea, stomatitis, fever) coincides with the Grade 3 neutropenic episode. If Grade 4 neutropenia occurs treatment with Xeloda should be interrupted until recovery to Grade 0-1. Treatment should only be readministered when the neutrophil count is $\geq 1.5 \times 10^9$/L (Grade 0-1).

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 the neutrophil count drops below 1.0×10^9/L or if the platelet count drops below 75×10^9/L, stop capecitabine. At recovery, restart capecitabine at full dose.

Dehydration:
Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated. If Grade 2 (or higher) dehydration occurs, Xeloda treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be those for the precipitating adverse event in accordance with the above guidelines.

2.2.1 Special Dosage Instructions

Pediatric use
The safety and efficacy of Xeloda in children and adolescents (< 18 years) have not been established.

Geriatric use
- For Xeloda monotherapy, no adjustment of the starting dose is needed. However, severe Grade 3 or 4 treatment-related ADRs were more frequent in patients ≥ 60 years of age compared to younger patients. Careful monitoring of patients ≥ 60 years of age is advisable.
- In combination with docetaxel, an increased incidence of Grade 3 or 4 treatment-related ADRs and treatment related serious adverse reactions were observed in patients 60 years of age or more (see section *3.1 Pharmacodynamic Properties*).

- For patients 60 years of age or more treated with the combination of Xeloda plus docetaxel, a starting dose reduction of Xeloda to 75% (950 mg/m^2 twice daily) is recommended. If no toxicity is observed in patients ≥ 60 years of age treated with a reduced Xeloda starting dose in combination with docetaxel, the dose of Xeloda may be cautiously escalated to 1250 mg/m^2 twice daily.

Renal impairment
Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockcroft and Gault] at baseline). The incidence of Grade 3 or 4 ADRs in patients with moderate renal impairment (creatinine clearance 30-50 mL/min at baseline) is increased compared to the overall population. In patients with moderate renal impairment at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m^2 is recommended. In patients with moderate renal impairment at baseline, no dose reduction is required for a starting dose of 1000 mg/m^2. In patients with mild renal impairment (creatinine clearance 51-80 mL/min at baseline) no adjustment of the starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3 or 4 ADRs during treatment and subsequent dose adjustment as outlined in the table above. These dose adjustment recommendations for renal impairment apply both to monotherapy and combination use (see also section *2.5.5 Geriatric Use*).

Hepatic impairment
Insufficient safety and efficacy data are available in patients with hepatic impairment to provide a dose adjustment recommendation. No information is available on hepatic impairment due to cirrhosis or hepatitis.

2.3 Contraindications
- Xeloda is contraindicated in patients with a known hypersensitivity to capecitabine or to any of its excipients.
- Xeloda is contraindicated in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil.
- Xeloda is contraindicated in patients with known complete absence of dihydropirimidine dehydrogenase (DPD) activity (see section *2.4 Warnings and Precautions*).
- Xeloda should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see section *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction).*
- Xeloda is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min).
- During pregnancy and lactation.
- In patients with severe leukopenia, neutropenia, or thrombocytopenia.
- In patients with severe hepatic impairment.
- If contraindications exist to any of the agents in a combination regimen, that agent should not be used.

2.4 Warnings and Precautions
Warnings
Dose limiting toxicities: Including diarrhoea, abdominal pain, nausea, stomatitis and hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia). Most ADRs are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced.

Diarrhoea: Xeloda can induce diarrhoea, which has been observed in 50% of patients. Patients with severe diarrhoea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. Standard antidiarrhoeal treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. NCIC CTC Grade 2 diarrhoea is defined as an increase of 4 to 6 stools/day or nocturnal stools, Grade 3 diarrhoea as an increase of 7 to 9 stools/day or incontinence and malabsorption. Grade 4 diarrhoea is an increase of ≥ 10 stools/day or grossly bloody diarrhoea or the need for parenteral support. If Grade 2, 3 or 4 diarrhoea occurs, administration of Xeloda should be immediately interrupted until the diarrhoea resolves or decreases in intensity to Grade 1. Following Grade 3 or 4 diarrhoea, subsequent doses of Xeloda should be decreased or treatment discontinued permanently (Grade 4).

Dehydration: Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhoea may rapidly become dehydrated.

Dehydration may cause acute renal failure, especially in patients with preexisting compromised renal function or when capecitabine is given concomitantly with known nephrotoxic agents. Fatal outcome of renal failure has been reported in these situations, see section *2.6.2 Postmarketing Experience, Undesirable Effects*.

If Grade 2 (or higher) dehydration occurs, Xeloda treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications should be applied for the precipitating ADR as necessary (see section *2.2 Dosage and Administration*)

Dihydropyrimidine dehydrogenase (DPD) deficiency: Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity, an enzyme involved in fluorouracil degradation.

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 section *2.3 Contraindications*).

Patients with certain heterozygous *DPYD* variants (e.g. *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 based on the local availability and current guidelines.

In patients with unrecognized 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 section *2.7 Overdose*).

Precautions

Cardiotoxicity: Cardiotoxicity has been associated with fluoropyrimidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes. These ADRs may be more common in patients with a prior history of coronary artery disease. Cardiac arrhythmias, angina pectoris, myocardial infarction, heart failure and cardiomyopathy have been reported in patients receiving Xeloda. Caution must be exercised in patients with history of significant cardiac disease, arrhythmias and angina pectoris (see section *2.6 Undesirable Effects*).

Xeloda can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN), see section *2.6.2 Postmarketing Experience, Undesirable Effects*. Xeloda should be permanently discontinued in patients who experience a severe skin reaction possibly attributable to Xeloda treatment.

Xeloda can induce hand–foot syndrome (also known as hand-foot skin reaction, palmar–plantar erythrodysesthesia or chemotherapy-induced acral erythema), which is a cutaneous toxicity. Persistent or severe hand-foot syndrome (Grade 2 and above) can eventually lead to loss of fingerprints, which could impact patient identification.

Grade 1 hand-foot syndrome is defined by numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities.

Grade 2 hand-foot syndrome is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living.

Grade 3 hand-foot syndrome is defined as moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living.

If Grade 2 or 3 hand-foot syndrome occurs, administration of Xeloda should be interrupted until the event resolves or decreases in intensity to Grade 1. Following Grade 3 hand-foot syndrome, subsequent doses of Xeloda should be decreased (see section 2.2 *Dosage and Administration*). When Xeloda and cisplatin are used in combination, use of vitamin B6 (pyridoxine) is not advised for the symptomatic or secondary prophylactic treatment of hand–foot syndrome, because of published reports that it may decrease the efficacy of cisplatin. There is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis in patients treated with Xeloda.

Hepatic impairment: Xeloda can induce hyperbilirubinemia. In the absence of safety and efficacy data in patients with hepatic impairment, Xeloda use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastasis. Administration of Xeloda should be interrupted if treatment-related elevations in bilirubin of > 3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2.5 x ULN occur. Treatment with Xeloda monotherapy may be resumed when bilirubin decreases to ≤ 3.0 x ULN or hepatic aminotransferases decrease to ≤ 2.5 x ULN. For combination treatment with Xeloda and docetaxel, see also section *2.2 Dosage and Administration*.

Hypo- or hypercalcemia: Hypo- or hypercalcemia has been reported during Xeloda treatment. Caution must be exercised in patients with preexisting hypo- or hypercalcaemia (see section *2.6 Undesirable Effects*).

Central or peripheral nervous system disease: Caution must be exercised in patients with central or peripheral nervous system disease, e.g. brain metastasis or neuropathy (see section *2.6 Undesirable Effects)*.

Diabetes mellitus or electrolyte disturbances: Caution must be exercised in patients with diabetes mellitus or electrolyte disturbances, as these may be aggravated during Xeloda treatment.

Coumarin-derivative anticoagulation: Care should be exercised when Xeloda is coadministered with 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 (see section *2.8 Interactions with Other Medicinal Products and Other Forms of Interaction*).

Renal impairment: The incidence of Grade 3 or 4 ADRs in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) is increased compared to the overall population (see sections *2.2 Dosage and Administration* and *2.3 Contraindications*).

As this medicinal product contains anhydrous lactose as an excipient, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

2.4.1 General

Patients treated with Xeloda should be carefully monitored for toxicity. Most ADRs are reversible and do not require permanent discontinuation of therapy, although doses may have to be withheld or reduced (see also section *2.2 Dosage and Administration*).

2.4.2 Drug Abuse and Dependence

Not applicable.

2.4.3 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 (see section *2.6 Undesirable Effects*).

2.5 Use in Special Populations

2.5.1 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 sections *3.3.3 Reproductive Toxicity* and *3.3.4 Impairment of Fertility*).

Contraception
Females
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Xeloda. 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.

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.

2.5.2 Pregnancy
There are no studies in pregnant women using Xeloda; however, based on the pharmacological and toxicological properties of Xeloda, it can be assumed that Xeloda may cause fetal harm if administered to pregnant women. In reproductive toxicity studies in animals, capecitabine administration caused embryolethality and teratogenicity. These findings are expected effects of fluoropyrimidine derivatives. Capecitabine should be considered a potential human teratogen. Xeloda should not be used during pregnancy (see section *3.3.4 Reproductive Toxicity*). If Xeloda is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient must be apprised of the potential hazard to the fetus.

2.5.3 Lactation
It is not known whether Xeloda is excreted in human milk. No studies have been conducted to assess the impact of Xeloda on milk production or its presence in human breast milk. As the potential for harm to the nursing infant is unknown, breastfeeding should be discontinued during treatment with Xeloda and for 2 weeks after the final dose.

2.5.4 Pediatric Use
The safety and efficacy of Xeloda in pediatric patients below the age of 18 have not been established.

2.5.5 Geriatric Use
Among patients with colorectal cancer aged 60–79 years receiving Xeloda monotherapy in the metastatic setting, the incidence of gastrointestinal toxicity was similar to that in the overall population. In patients aged 80 years or older, a larger percentage experienced reversible Grade 3 or 4 gastrointestinal ADRs, such as diarrhoea, nausea and vomiting (see section *2.2.1 Special Dosage Instructions*). When Xeloda was used in combination with other agents elderly patients (≥ 65 years) experienced more Grade 3 and Grade 4 ADRs and ADRs that led to discontinuation than younger patients. An analysis of safety data in patients equal to or greater than 60 years of age treated with Xeloda plus docetaxel combination therapy showed an increase in the incidence of treatment-related Grade 3 and 4 ADRs, treatment-related serious adverse events and early withdrawals from treatment due to adverse events compared to patients less than 60 years of age.

2.5.6 Renal Impairment
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 ADRs was higher in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) (see section *2.2.1 Special Dosage Instructions*).

2.5.7 Hepatic Impairment
Patients with hepatic impairment should be carefully monitored when Xeloda is administered. The effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of Xeloda is not known (see sections *3.2.5 Pharmacokinetics in Special Populations* and *2.2.1 Special Dosage Instructions*).

2.6 Undesirable Effects
2.6.1 Clinical Trials
The adverse drug reactions (ADRs) considered to be possibly, probably, or remotely related to the administration of Xeloda have been obtained from clinical studies in > 2000 patients conducted with Xeloda monotherapy (in adjuvant therapy of colon cancer, in metastatic colorectal cancer and metastatic breast cancer), Xeloda in combination with docetaxel in metastatic breast cancer after failure of cytotoxic chemotherapy and Xeloda in combination with various agents in advanced gastric cancer. The safety data from the clinical trial population for monotherapy and combination therapy are presented in this section. For postmarketing experience see below. See section *3.1 Pharmacodynamic Properties* for details of major studies, including study designs and major efficacy results.

The most commonly reported treatment-related adverse drug reactions were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), fatigue and hand-foot syndrome (palmar-plantar erythrodysesthesia).

The following headings are used to rank the adverse drug reactions by frequency: very common (≥ 1/10), common (≥ 1/100, < 1/10) and uncommon (≥ 1/1000, < 1/100). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Xeloda Monotherapy:
Safety data for Xeloda monotherapy has been obtained from > 1900 patients. Table 4 lists adverse drug reactions associated with the use of Xeloda monotherapy in three major clinical trials in adjuvant treatment for colon cancer and for metastatic colorectal cancer. Each adverse drug reaction has been added to the appropriate frequency grouping according to the overall incidence from a pooled analysis of the safety data from these three major clinical studies in colorectal cancer.

The most frequently reported treatment-related adverse drug reactions were gastrointestinal disorders, especially diarrhoea, nausea, vomiting, stomatitis, and hand-foot syndrome (palmar-plantar erythrodysesthesia). The safety profiles of Xeloda monotherapy for the metastatic breast cancer, metastatic colorectal cancer and adjuvant colon cancer populations are comparable.

Table 4 Summary of adverse drug reactions reported in patients treated with Xeloda monotherapy in adjuvant treatment for colon cancer and metastatic colorectal cancer

Body System	Very Common (≥ 1/10) All Grades	Common (≥ 1/100 - < 1/10) All Grades	Uncommon (≥ 1/1000 - < 1/100) Severe and/or Life-threatening (Grade 3-4) or Considered Medically Relevant
Infections and infestations		Herpes simplex Nasopharyngitis Lower respiratory tract infection	Sepsis Urinary tract infection Cellulitis Tonsillitis Pharyngitis Oral candidiasis Influenza Gastroenteritis Fungal infection Herpes infection Infection Tooth abscess
Neoplasm benign, malignant and unspecified	-	-	Lipoma
Blood and lymphatic system disorders	-	Neutropenia Anemia	Febrile neutropenia Pancytopenia Granulocytopenia Thrombocytopenia Leukopenia Hemolytic anemia
Immune system disorders	-	-	Hypersensitivity
Metabolism and nutrition disorders	Anorexia	Dehydration Decreased appetite	Diabetes Hypokalemia Appetite disorder Malnutrition Hypertriglyceridemia
Psychiatric disorders	-	Insomnia Depression	Confusional state Panic attack Depressed mood Libido decreased
Nervous system disorders	-	Headache Lethargy Dizziness Parasthesia Dysgeusia	Aphasia Memory impairment Ataxia Syncope Balance disorder Sensory disorder Neuropathy peripheral
Eye disorders	-	Lacrimation increased Conjunctivitis Eye irritation	Visual acuity reduced Diplopia
Ear and labyrinth	-	-	Vertigo

disorders			Ear pain
Cardiac disorders	-	-	Angina unstable Angina pectoris Myocardial ischemia Atrial fibrillation Arrhythmia Tachycardia Sinus tachycardia Palpitations
Vascular disorders	-	Thrombophlebitis	Deep vein thrombosis Hypertension Petechiae Hypotension Hot flush Peripheral coldness
Respiratory, thoracic and mediastinal disorders	-	Dyspnoea Epistaxis Cough Rhinorrhea	Pulmonary embolism Pneumothorax Haemoptysis Asthma Dyspnoea exertional
Gastrointestinal disorders	Diarrhoea Vomiting Nausea Stomatitis* Abdominal pain	Gastrointestinal haemorrhage Constipation Upper abdominal pain Dyspepsia Flatulence Dry mouth Loose stools	Intestinal obstruction Ascites Enteritis Gastritis Dysphagia Abdominal pain lower Oesophagitis Abdominal discomfort Gastroesophageal reflux disease Colitis
Hepatobiliary disorders	-	Hyperbilirubinemia /blood bilirubin/blood bilirubin increased	Jaundice
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome**	Rash Alopecia Erythema Dry skin Pruritus Skin hyperpigmentation Rash macular Skin desquamation Dermatitis Pigmentation disorder Nail disorder	Skin ulcer Rash Urticaria Photosensitivity reaction Palmar erythema Swelling face Purpura
Muskuloskeletal and connective tissue disorders	-	Pain in extremity Back pain Arthralgia	Joint swelling Bone pain Facial pain Musculoskeletal stiffness Muscular weakness
Renal and urinary disorders	-	-	Hydronephrosis Urinary incontinence Haematuria Nocturia

Reproductive system and breast disorders	-	-	Vaginal haemorrhage
General disorders and administration site conditions	Fatigue Asthenia	Pyrexia Lethargy Oedema peripheral Malaise Non-cardiac chest pain	Oedema Chills Influenza-like illness Rigors
Investigations	-	Weight decreased Liver function test abnormalities	Blood in stool International normalised ratio increased Blood creatinine increased Body temperature increased
Injury, poisoning and procedural complications	-	-	Blister Overdose

* Stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration.
** Based on the postmarketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints (see section *2.4 Warnings and Precautions*).

Laboratory Abnormalities observed with Xeloda Monotherapy:
Table 5 lists laboratory abnormalities of all grades observed with Xeloda monotherapy in three major trials in adjuvant treatment for colon cancer and for metastatic colorectal cancer. Each laboratory abnormality has been added to the appropriate frequency grouping according to the overall incidence from a pooled analysis of the safety data from these three major clinical studies in colorectal cancer.

Table 5 Laboratory abnormalities observed in patients treated with Xeloda monotherapy

Grade of Abnormality	**Very Common (≥ 1/10)**	**Common (≥ 1/100 - < 1/10)**	**Uncommon (≥ 1/1000 - < 1/100)**
Patients with Grade 1 to 4 abnormality	Decreased haemoglobin Decreased neutrophils/granulocytes Decreased platelets Decreased lymphocytes Decreased sodium Decreased potassium Decreased calcium Increased bilirubin Increased alkaline phosphatase Increased ALAT (SGPT) Increased ASAT (SGOT)	Increased calcium	-
Patients with Grade 3/4	Decreased lymphocytes Increased bilirubin	Decreased haemoglobin Decreased neutrophils/granulocytes Decreased platelets Decreased calcium	Decreased sodium Decreased potassium Increased calcium Increased ASAT (SGOT)

		Increased alkaline phosphatase Increased ALAT (SGPT)	
Patients with Grade 4	-	Decreased neutrophils/granulocytes Decreased lymphocytes Decreased calcium Increased bilirubin	Decreased haemoglobin Decreased platelets Decreased sodium Decreased potassium Increased calcium Increased alkaline phosphatase Increased ALAT (SGPT) Increased ASAT (SGOT)

Xeloda in combination with cisplatin:
Safety data for Xeloda in combination with cisplatin has been obtained from > 150 patients. Table 6 lists adverse drug reactions associated with the use of Xeloda in combination with cisplatin in the major clinical trial in gastric cancer. The adverse drug reactions shown are those that were seen **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy. Each adverse drug reaction has been added to the appropriate frequency grouping according to the incidence seen in the major clinical trial.

The incidence of hand-foot syndrome for Xeloda plus cisplatin was 22% (all grades) and 4% (Grade 3) in study ML17032 (see section *3.1 Pharmacodynamic Properties*).

Table 6 Summary of related adverse drug reactions reported in patients treated with Xeloda in combination with cisplatin in addition to those seen with Xeloda monotherapy or seen at a higher frequency grouping compared to Xeloda monotherapy

Body System	**Very common (≥ 1/10)** **All Grades**	**Common (≥ 1/100 - < 1/10)** **All Grades**	**Uncommon (≥ 1/1000 - < 1/100)** **Severe and/or Life-threatening (Grade 3-4) or Considered Medically Relevant**
Infections and infestations	-	Herpes zoster Urinary tract infection	-
Neoplasm benign, malignant and unspecified	-	-	Aleukaemic leukaemia
Blood and lymphatic system disorders	Neutropenia Leukopenia Anemia	Thrombocytopenia Bone marrow depression	-
Metabolism and nutrition disorders	-	Hypokalemia Hyponatremia	Hyponatremia Dehydration Hyperglycemia Decreased appetite
Psychiatric disorders	-	Sleep disorder	-

Nervous system disorders	-	Neuropathy Peripheral sensory neuropathy Hypoaesthesia	Dizziness
Ear and labyrinth disorders	-	Tinnitus Hypoacusis	-
Gastrointestinal disorders	-	Upper gastrointestinal haemorrhage Mouth ulceration Gastritis	Constipation Abdominal pain
Hepatobiliary disorders	-	Abnormal hepatic function	-
Skin and subcutaneous tissue disorders	-	Hyperhidrosis	-
Musculoskeletal and connective tissue disorders	-	Myalgia	-
Renal and urinary disorders	-	-	Renal failure Acute renal failure
General disorders and administration site conditions	-	Mucosal inflammation	Fatigue Malaise
Investigations	-	Creatinine renal clearance decreased	-

Xeloda in combination with docetaxel:
Safety data for Xeloda in combination with docetaxel has been obtained from > 250 patients. Table 7 lists adverse drug reactions associated with the use of Xeloda in combination with docetaxel in the major clinical trial in metastatic breast cancer. The adverse drug reactions shown are those that were seen **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy. Each adverse drug reaction has been added to the appropriate frequency grouping according to the incidence seen in the major clinical trial.

Table 7 Summary of related adverse drug reactions reported in patients treated with Xeloda in combination with docetaxel in addition to those seen with Xeloda monotherapy or seen at a higher frequency grouping compared to Xeloda monotherapy

Body System	**Very common (≥ 1/10)** **All Grades**	**Common (≥ 1/100 - < 1/10)** **All Grades**	**Uncommon (≥ 1/1000 - < 1/100)** **Severe and/or Life-threatening (Grade 3-4) or Considered Medically Relevant**
Infections and infestations	-	Oral candidiasis	-
Blood and lymphatic system disorders	Neutropenic fever (Grade 3-4)	-	-
Metabolism and nutrition disorders	Appetite decreased	-	-
Nervous system	Taste disturbance	Peripheral neuropathy	Headache

disorders	Paresthesia		
Eye disorders	Lacrimation increased	-	-
Vascular disorders	Lower limb oedema	-	-
Respiratory, thoracic and mediastinal system disorders	Sore throat	-	Epistaxis Cough
Gastrointestinal disorders	Constipation Dyspepsia	-	-
Skin and subcutaneous tissue disorders	Alopecia Nail disorder	Rash erythematous Nail discoloration Onycholysis	-
Musculoskeletal and connective tissue disorders	Myalgia Arthralgia	-	-
General disorders and administration site	Pyrexia Weakness	Pain in limb Pain	-

Xeloda in combination with oxaliplatin:
Adverse drug reactions reported in patients treated with Xeloda in combination with oxaliplatin **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy include: *Very common adverse drug reactions:* anemia, leukopenia, neutropenia, thrombocytopenia, neuropathy; *Common adverse drug reactions:* bleeding.

Xeloda in combination with epirubicin and oxaliplatin:
Grade 3 and Grade 4 adverse drug reactions reported in patients treated with Xeloda in combination with epirubicin and oxaliplatin **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy include: *Very common, Grade 3 and Grade 4 adverse drug reactions*: leukopenia, neutropenia, lethargy; *Common, Grade 3 and Grade 4 adverse drug reactions:* anemia, thrombocytopenia, febrile neutropenia, peripheral neuropathy, infection, fever, thromboembolism.

Xeloda in combination with epirubicin and cisplatin:
Grade 3 and Grade 4 adverse drug reactions reported in patients treated with Xeloda in combination with epirubicin and cisplatin **in addition to** those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy include: *Very common, Grade 3 and Grade 4 adverse drug reactions*: leukopenia, neutropenia, anemia, lethargy, thromboembolism; *Common, Grade 3 and Grade 4 adverse drug reactions:* thrombocytopenia, febrile neutropenia, peripheral neuropathy, infection, fever.

2.6.2 Postmarketing Experience
The following ADRs have been identified during postmarketing experience with Xeloda based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥ 1/10), common (≥ 5/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (≥ 1/1000 to < 1/100), unknown (cannot be estimated from the available data):

Table 8 Adverse drug reactions from postmarketing experience

System Organ Class (SOC)	ADR(s)	Frequency
Renal and urinary disorders	Acute renal failure secondary to dehydration see section *2.4 Warnings and Precautions*	*Rare*
Nervous system disorders	Toxic leukoencephalopathy	*Unknown*
Hepatobiliary disorders	Hepatic failure, Cholestatic hepatitis	*Very rare*
Metabolism and nutrition disorders	Hypertriglyceridemia	*Uncommon*
Skin and subcutaneous tissue disorders	Cutaneous lupus erythematosus, Severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN), see section *2.4 Warnings and Precautions*	*Very rare*
Eye disorders	Lacrimal duct stenosis NOS, Corneal disorders including keratitis	*Very rare*
Immune system disorders	Angioedema*	*Unknown*
* This subtype of hypersensitivity reaction (section 2.6.1) was reported in the postmarketing setting.		

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, diarrhoea, nausea, gastric irritation, and vomiting

2.7 Overdose
The manifestations of acute overdose include nausea, vomiting, diarrhoea, mucositis, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

2.8 Interactions with Other Medicinal Products and Other Forms of Interaction
Interaction studies have only been performed in adults.

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 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. Since metabolism of R-warfarin was not affected, these results indicate that capecitabine down-regulates isozyme 2C9, but has no effect on isozymes 1A2 and 3A4.

These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. 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 section *2.4 Warnings and Precautions).*

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 coadministered with these drugs.

Phenytoin
Increased phenytoin plasma concentrations have been reported during concomitant use of Xeloda with phenytoin. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine (see *Coumarin anticoagulants*). Patients taking phenytoin concomitantly with Xeloda should be regularly monitored for increased phenytoin plasma concentrations.

Drug-food interaction
In all clinical trials, patients were instructed to take Xeloda within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that Xeloda be administered with food. Administration with food decreases the rate of capecitabine absorption (see section *3.2 Pharmacokinetic Properties*).

Antacid
The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of Xeloda was investigated in 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 (folinic acid)
A combination study with Xeloda and folinic acid indicated that folinic acid has no major effect on the pharmacokinetics of Xeloda and its metabolites. However, folinic acid has an effect on the pharmacodynamics of Xeloda and its toxicity may be enhanced by leucovorin: the maximum tolerated dose (MTD) of Xeloda alone using the intermittent regimen is 3000 mg/m^2 per day whereas it is only 2000 mg/m^2 per day when Xeloda was combined with folinic acid (30 mg orally bid).

Sorivudine and analogues
A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine, has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, Xeloda should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see section *2.3 Contraindications*). There must be at least a 4-week waiting period between the end of treatment with sorivudine or its chemically related analogues, such as brivudine and start of Xeloda therapy.

Oxaliplatin
No clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occur when capecitabine and oxaliplatin were administered in combination, with or without bevacizumab.

Bevacizumab
There was no clinically significant effect of bevacizumab on the pharmacokinetic parameters of capecitabine or its metabolites.

Allopurinol
Interactions with allopurinol have been observed for 5-FU; with possible decreased efficacy of 5-FU. Concomitant use of allopurinol with Xeloda should be avoided.

Interaction with cytochrome P450
For potential interactions with isozymes 1A2, 2C9 and 3A4, see interactions with coumarin-derivative anticoagulation.

Interferon alpha
The MTD of Xeloda was 2000 mg/m^2 per day when combined with interferon alpha-2a (3 MIU/m^2 per day) compared to 3000 mg/m^2 per day when Xeloda was used alone.

Radiotherapy
The MTD of Xeloda alone using the intermittent regimen is 3000 mg/m^2 per day, whereas, when combined with radiotherapy for rectal cancer, the MTD of Xeloda is 2000 mg/m^2 per day using either a continuous schedule or given daily Monday through Friday during a 6-week course of radiotherapy.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps (see section *3.2 Pharmacokinetics Properties*). The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumor tissues, but also in normal tissues, albeit usually at lower levels. 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.

There is evidence that the metabolism of 5-FU in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, thereby interfering with the synthesis of deoxyribonucleic acid (DNA). The incorporation of 5-FU also leads to inhibition of RNA and protein synthesis. Since DNA and RNA are essential for cell division and growth, the effect of 5-FU may be to create a thymidine deficiency that provokes unbalanced growth and death of a cell. The effects of DNA and RNA deprivation are most marked on those cells which proliferate more rapidly and which metabolise 5-FU at a more rapid rate.

3.1.2 Clinical/Efficacy Studies

Colon and colorectal cancer:

Adjuvant therapy with Xeloda in colon cancer
Data from one multicentre, randomized, controlled 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 colon cancer (XACT Study). In this trial, 1987 patients were randomized to treatment with 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) or 5-FU and leucovorin (Mayo regimen: 20 mg/m^2 leucovorin IV followed by 425 mg/m^2 IV bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks). Xeloda was at least equivalent to IV 5-FU/LV in disease-free survival in per protocol population (hazard ratio 0.89; 95% CI 0.76-1.04). In the all-randomized population, tests for difference of Xeloda vs 5-FU/LV in disease-free and overall survival showed hazard ratios of 0.87 (95% CI 0.75–1.00; p=0.053) and 0.84 (95% CI 0.69–1.01; p=0.071), respectively. Relapse-free survival, censoring patients at the time of last tumor assessment in case of death unrelated to disease progression or

unrelated to treatment (for disease-free survival these death cases were considered as events), was statistically different in favour of Xeloda comparing to 5-FU/LV [HR 0.86 (95% CI 0.74–0.99; p=0.041)]. The median follow up at the time of the analysis was 3.8 years.

Monotherapy with Xeloda in metastatic colorectal cancer
Two identically designed, multicenter, randomized, controlled, phase 3 clinical trials have been conducted studying the use of Xeloda for first-line treatment of metastatic colorectal cancer (SO14695; SO14796). In these trials, 603 patients were randomized to treatment with Xeloda (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period and given as 3-week cycles) and 604 patients were randomized to treatment with 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).

The overall objective response rates in the all-randomized population (investigator assessment) were 25.7% (Xeloda) vs 16.7% (Mayo regimen); p < 0.0002. The median time to progression was 140 days (Xeloda) vs 144 days (Mayo regimen). Median survival was 392 days (Xeloda) vs 391 days (Mayo regimen). Currently, no comparative data are available on Xeloda monotherapy in colorectal cancer in comparison with first-line combination regimens.

Advanced gastric cancer:
Data from a multicentre, randomized, controlled phase III clinical trial in patients with advanced gastric cancer supports the use of Xeloda for treatment of advanced gastric cancer (ML17032). In this trial, 160 patients were randomized to treatment with Xeloda (1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period) and cisplatin (80 mg/m^2 as a 2-hour infusion every 3 weeks). A total of 156 patients were randomized to treatment with 5-FU (800 mg/m^2 per day, continuous infusion on days 1 to 5 every 3 weeks) and cisplatin (80 mg/m^2 as a 2-hour infusion on day 1, every 3 weeks). Xeloda in combination with cisplatin was non-inferior to 5-FU in combination with cisplatin in terms of progression-free survival in the per protocol analysis (hazard ratio 0.81; 95% CI 0.63-1.04). The median progression-free survival was 5.6 months (Xeloda + cisplatin) vs 5.0 months (5-FU + cisplatin). The hazard ratio for duration of survival (overall survival) was similar to the hazard ratio for progression-free survival (hazard ratio 0.85; 95% CI 0.64-1.13). The median duration of survival was 10.5 months (Xeloda + cisplatin) vs 9.3 months (5-FU + cisplatin).

Breast cancer:
Combination therapy with Xeloda and docetaxel in locally advanced or metastatic breast cancer
Data from one multicentre, randomized, controlled phase III clinical trial support the use of Xeloda in combination with docetaxel for treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy, including an anthracycline. In this trial, 255 patients were randomized to treatment with Xeloda (1250 mg/m^2 twice daily for 2 weeks followed by 1-week rest period and docetaxel 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks). 256 patients were randomized to treatment with docetaxel alone (100 mg/m^2 as a 1 hour intravenous infusion every 3 weeks). Survival was superior in the Xeloda + docetaxel combination arm (p=0.0126). Median survival was 442 days (Xeloda + docetaxel) vs 352 days (docetaxel alone). The overall objective response rates in the all-randomized population (investigator assessment) were 41.6% (Xeloda + docetaxel) vs 29.7% (docetaxel alone); p=0.0058. Time to progressive disease was superior in the Xeloda + docetaxel combination arm (p < 0.0001). The median time to progression was 186 days (Xeloda + docetaxel) vs 128 days (docetaxel alone).

Monotherapy with Xeloda after failure of taxanes, anthracycline containing chemotherapy, and for whom anthracycline therapy is not indicated
Data from two multicentre phase II clinical trials support the use of Xeloda monotherapy for treatment of patients after failure of taxanes and an anthracycline-containing chemotherapy regimen or for whom further anthracycline therapy is not indicated. In these trials, a total of 236 patients were treated with Xeloda (1250 mg/m^2 twice daily for 2 weeks followed by 1-week rest period). The overall objective response rates (investigator assessment) were 20% (first trial) and 25% (second trial). The median time to progression was 93 and 98 days. Median survival was 384 and 373 days.

General:
An analysis of safety data in patients treated with Xeloda monotherapy (colorectal cancer) with baseline renal impairment showed an increase in the incidence of treatment-related grade 3 and 4 ADRs compared to patients with normal renal function (36% in patients without renal impairment n=268, vs 41% in mild n=257 and 54% in moderate n=59, respectively) (see section *3.2 Pharmacokinetic Properties*). Patients with moderately impaired renal function show an increased rate of dose reduction (44%) vs 33% and 32% in patients with no or mild renal impairment and an increase in early withdrawals from treatment (21% withdrawals during the first two cycles) vs 5% and 8% in patients with no or mild renal impairment.

An analysis of safety data in patients ≥ 60 years of age treated with Xeloda monotherapy and an analysis of patients treated with Xeloda plus docetaxel combination therapy showed an increase in the incidence of treatment-related Grade 3 and 4 ADRs and treatment-related serious ADRs compared to patients < 60 years of age. Patients ≥ 60 years of age treated with Xeloda plus docetaxel also had more early withdrawals from treatment due to ADRs compared to patients < 60 years of age.

3.1.3 Immunogenicity
Not applicable.

3.2 Pharmacokinetic Properties
The pharmacokinetics of capecitabine have been evaluated over a dose range of 502-3514 mg/m^2/day. The parameters of capecitabine, 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (5'-DFUR) measured on days 1 and 14 were similar. The AUC of 5-FU was 30%-35% higher on day 14. Capecitabine dose reduction decreases systemic exposure to 5-FU more than dose-proportionally, due to nonlinear pharmacokinetics for the active metabolite.

3.2.1 Absorption
After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption but has only a minor effect on the areas under the curve (AUC) of 5'-DFUR and the subsequent metabolite 5-FU. At the dose of 1250 mg/m^2 on day 14 with administration after food intake, the peak plasma concentrations (C_{max} in µg/mL) for capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 4.47, 3.05, 12.1, 0.95 and 5.46, respectively. The times to peak plasma concentrations (T_{max} in hours) were 1.50, 2.00, 2.00, 2.00 and 3.34. The $AUC_{0-\infty}$ values in µg·h/mL were 7.75, 7.24, 24.6, 2.03 and 36.3.

3.2.2 Distribution
Protein binding
In vitro human plasma studies have determined that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound, mainly to albumin.

3.2.3 Metabolism

Capecitabine is first metabolised by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumor tissues. Further catalytic activation of 5'-DFUR then occurs by thymidine phosphorylase (ThyPase). The enzymes involved in the catalytic activation are found in tumor tissues but also in normal tissues, albeit usually at lower levels. The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations within tumor tissues. In the case of colorectal tumors, 5-FU generation appears to be in large part localised in tumor stromal cells. Following oral administration of capecitabine to patients with colorectal cancer, the ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 3.2 (ranged from 0.9 to 8.0). The ratio of 5-FU concentration in tumor to plasma was 21.4 (ranged from 3.9 to 59.9, n=8) whereas the ratio in healthy tissues to plasma was 8.9 (ranged from 3.0 to 25.8, n=8). Thymidine phosphorylase activity was measured and found to be 4 times greater in primary colorectal tumor than in adjacent normal tissue. According to immunohistochemical studies, thymidine phosphorylase appears to be in large part localised in tumor stromal cells.

5-FU is further catabolised by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureidopropionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is the rate limiting step. Deficiency of DPD may lead to increased toxicity of capecitabine (see sections *2.3 Contraindications* and *2.4 Warnings and Precautions*).

3.2.4 Elimination

The elimination half-lives ($t_{1/2}$ in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 0.85, 1.11, 0.66, 0.76 and 3.23, respectively. Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Faecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL, which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

Combination therapy

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).

3.2.5 Pharmacokinetics in Special Populations

A population pharmacokinetic analysis was carried out after Xeloda treatment of 505 patients with colorectal cancer dosed at 1250 mg/m^2 twice daily. Gender, 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.

Hepatic impairment due to liver metastases

According to a pharmacokinetic study in cancer patients with mild to moderate liver impairment due to liver metastases, the bioavailability of capecitabine and exposure to 5-FU may increase compared to patients with no liver impairment. No formal pharmacokinetic study has been conducted and no population pharmacokinetic data was collected in patients with severe hepatic impairment.

Renal impairment
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 (see section *2.2.1 Special Dosage Instructions*).

Geriatric population
Based on a population pharmacokinetic analysis that included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients greater than or equal to 65 years, 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 sections 2.2.1 *Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*, subsection *Renal Impairment*).

Race
Following oral administration of 825 mg/m^2 capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower C_{max} and 24% lower AUC for capecitabine than Caucasian patients (n=22). Japanese patients had also about 25% lower C_{max} and 34% lower AUC for FBAL than Caucasian patients. The clinical relevance of these differences is unknown. No significant differences occurred in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU).

3.3 Nonclinical Safety
In repeat-dose toxicity studies, daily oral administration of capecitabine to cynomolgus monkeys and mice produced toxic effects on the gastrointestinal, lymphoid and haemopoietic systems, typical for fluoropyrimidines. These toxicities were reversible. Skin toxicity, characterised by degenerative/regressive changes, was observed with capecitabine. Capecitabine was devoid of hepatic and CNS toxicities. Cardiovascular toxicity (e.g. PR- and QT-interval prolongation) was detectable in cynomolgus monkeys after intravenous administration (100 mg/kg) but not after repeated oral dosing (1379 mg/m^2/day).

3.3.1 Carcinogenicity
A two-year mouse carcinogenicity study produced no evidence of carcinogenicity by capecitabine.

3.3.2 Genotoxicity
Capecitabine was not mutagenic *in vitro* to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). However, similar to other nucleoside analogues (i.e. 5-FU), capecitabine was clastogenic in human lymphocytes (*in vitro*) and a positive trend occurred in mouse bone marrow micronucleus tests (*in vivo*).

3.3.3 Reproductive Toxicity
In embryotoxicity and teratogenicity studies in mice, dose-related increases in fetal resorption and teratogenicity were observed. In monkeys, abortion and embryolethality were observed at high doses, but there was no evidence of teratogenicity.

Oral administration of capecitabine to pregnant mice during the period of organogenesis at a dose of 198 mg/kg/day caused malformations and embryolethality. In separate pharmacokinetic

studies, this dose in mice produced 5'-DFUR AUC values that were approximately 0.2 times the AUC values in patients administered the recommended daily dose. Oral administration of capecitabine to pregnant monkeys during the period of organogenesis at a dose of 90 mg/kg/day, caused fetal lethality. This dose produced 5'-DFUR AUC values that were approximately 0.6 times the AUC values in patients administered the recommended daily dose.

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

3.3.5 Other
Not applicable.

4. PHARMACEUTICAL PARTICULARS

4.1 Storage
Do not store above 30^0 C, store in the original package in order to protect from moisture.
This medicine should not be used after the expiry date (EXP) shown on the pack.

4.2 Special Instructions for Use, Handling and Disposal
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.

PACKS
Box, 12 blisters @ 10 film-coated tablets Reg. No.: DKI2157510817A1

Medicine: keep out of reach and sight of children
On medical prescription only
Harus dengan resep dokter

Manufactured by:
Excella GmbH & Co. KG, Feucht, Germany
for CHEPLAPHARM Arzneimittel GmbH, Greifswald, Germany

Registered by:
PT Menarini Indria Laboratories
Bekasi, Indonesia

INFORMASI PRODUK UNTUK PASIEN

XELODA
Capecitabine
Tablet salut selaput
500 mg

Bacalah seluruh brosur ini dengan saksama sebelum Anda mulai menggunakan obat ini karena brosur ini berisi informasi yang penting bagi Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya lagi.
- Bila Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, apoteker atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Jangan memberikannya kepada orang lain. Obat ini dapat membahayakan mereka, walaupun tanda-tanda penyakit mereka serupa dengan penyakit Anda.
- Bila Anda mengalami efek samping, bicarakanlah dengan dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi di luar dari apa yang tercantum pada brosur ini. Lihat bagian 4.

Apa yang terdapat di dalam brosur ini

1. Apa itu Xeloda dan kegunaannya
2. Apa yang perlu Anda ketahui sebelum mengonsumsi Xeloda
3. Bagaimana cara mengonsumsi Xeloda
4. Efek samping yang mungkin terjadi
5. Bagaimana cara penyimpanan Xeloda
6. Isi kemasan dan informasi lainnya

1. Apa itu Xeloda dan kegunaannya

Xeloda termasuk dalam kelompok obat yang disebut "obat sitostatik", yang menghentikan pertumbuhan sel kanker. Xeloda mengandung *capecitabine*, yang mana bukan obat sitostatik itu sendiri. Setelah diserap oleh tubuh, maka *capecitabine* berubah menjadi obat antikanker yang aktif (lebih banyak dalam jaringan tumor daripada dalam jaringan normal).
Xeloda digunakan dalam pengobatan kanker kolon, rektum, lambung, atau payudara.
Xeloda digunakan untuk mencegah terjadinya kekambuhan kanker kolon setelah pembuangan tumor seluruhnya dengan pembedahan.
Xeloda dapat digunakan sendiri atau dikombinasikan dengan obat lain.

2. Apa yang perlu Anda ketahui sebelum mengonsumsi Xeloda

Jangan mengonsumsi Xeloda:

- jika Anda alergi terhadap *capecitabine* atau bahan tambahan lain dari obat ini (tercantum pada bagian 6). Anda harus memberi tahu dokter Anda jika Anda mengetahui bahwa Anda memiliki alergi terhadap obat ini,
- jika sebelumnya Anda pernah mengalami reaksi serius dengan terapi *fluoropyrimidine* (suatu kelompok obat antikanker seperti *fluorouracil*),
- jika Anda hamil atau menyusui,
- jika tingkat sel darah putih atau trombosit dalam darah Anda sangat rendah (leukopenia, neutropenia atau trombositopenia),

- jika Anda memiliki gangguan hati atau ginjal berat,
- jika Anda memiliki gangguan aktivitas enzim *dihydropyrimidine dehydrogenase* (DPD) total,
- jika Anda sedang mendapatkan pengobatan saat ini atau telah mendapatkan perawatan dalam 4 minggu terakhir dengan brivudin, sorivudin atau zat dengan kelas yang sama sebagai bagian dari terapi herpes zoster (cacar ular atau api).

Peringatan dan perhatian

Sampaikan kepada dokter, perawat atau apoteker Anda sebelum menggunakan Xeloda

- jika Anda mengetahui bahwa Anda memiliki defisiensi parsial enzim *dihydropyrimidine dehydrogenase* (DPD)
- jika Anda memiliki gangguan hati atau ginjal
- jika Anda memiliki atau pernah memiliki gangguan jantung (misalnya denyut jantung tidak teratur atau nyeri dada, rahang dan punggung yang disebabkan oleh kegiatan fisik dan karena gangguan pada aliran darah ke jantung)
- jika Anda menderita penyakit otak (misalnya kanker yang telah menyebar ke otak, atau kerusakan saraf (neuropati))
- jika Anda memiliki ketidakseimbangan kalsium (ditunjukkan oleh pengujian darah)
- jika Anda menderita diabetes
- jika Anda tidak dapat menjaga makanan atau air dalam tubuh disebabkan oleh mual dan muntah yang parah
- jika Anda menderita diare
- jika Anda dehidrasi
- jika Anda mengalami ketidakseimbangan ion dalam darah (ketidakseimbangan elektrolit, ditunjukkan oleh pengujian)
- jika Anda memiliki riwayat penyakit mata sehingga Anda memerlukan pemantauan ekstra pada mata Anda
- jika Anda mengalami reaksi kulit yang parah.

Defisiensi DPD: Defisiensi DPD adalah kondisi langka yang muncul saat lahir yang tidak berhubungan dengan masalah kesehatan kecuali Anda menerima obat tertentu. Jika Anda mengalami defisiensi DPD yang tidak diketahui dan menggunakan Xeloda, maka Anda lebih berisiko untuk mengalami efek samping akut yang serius yang tercantum pada bagian 4 Kemungkinan Efek Samping. Hubungi dokter Anda segera jika Anda khawatir tentang adanya efek samping atau jika Anda mendapati efek samping tambahan yang tidak tercantum pada brosur ini (lihat bagian 4 Kemungkinan Efek Samping).

Anak dan remaja

Xeloda tidak diindikasikan untuk anak dan remaja. Xeloda tidak boleh diberikan kepada anak dan remaja.

Obat-obatan lain dan Xeloda

Sebelum memulai pengobatan, sampaikan kepada dokter, perawat atau apoteker Anda jika Anda sedang menggunakan, baru saja menggunakan, atau mungkin menggunakan obat lain. Hal ini sangat penting, karena menggunakan lebih dari satu obat pada saat yang bersamaan dapat memperkuat atau memperlemah efek obat. Anda harus sangat berhati-hati jika menggunakan salah satu obat berikut:

- obat asam urat (alopurinol),

- obat pengencer darah (kumarin, warfarin),
- obat antivirus tertentu (sorivudin dan brivudin),
- obat untuk kejang atau tremor (fenitoin),
- interferon alfa,
- radioterapi dan obat tertentu yang digunakan untuk mengobati kanker (asam folinat, oxaliplatin, bevacizumab, cisplatin, irinotecan),
- obat yang digunakan untuk mengobati defisiensi asam folat.

Xeloda dengan makanan dan minuman
Anda harus meminum Xeloda dalam waktu tidak lebih dari 30 menit setelah makan.

Kehamilan dan menyusui
Sebelum memulai pengobatan, Anda harus memberi tahu dokter Anda jika Anda hamil, berpikir bahwa Anda mungkin hamil, atau sedang merencanakan kehamilan. Xeloda tidak boleh diberikan pada ibu hamil, diduga hamil, ataupun ibu menyusui.

Mengemudi dan menggunakan mesin
Xeloda dapat membuat Anda pusing, mual atau lelah. Oleh karena itu, Xeloda dapat memengaruhi kemampuan Anda untuk mengendarai mobil atau mengoperasikan mesin.

Xeloda mengandung laktosa anhidrat
Jika Anda mengetahui bahwa Anda memiliki intoleransi terhadap beberapa macam gula, seperti laktosa hubungi dokter Anda sebelum menggunakan obat ini.

3. Bagaimana cara mengonsumsi Xeloda
Selalu gunakan obat ini tepat seperti yang diberitahukan oleh dokter, perawat atau apoteker Anda. Cek kepada dokter, perawat atau apoteker Anda jika Anda tidak yakin.
Xeloda hanya boleh diresepkan oleh dokter yang berpengalaman dalam penggunaan obat antikanker.

Dokter Anda akan meresepkan dosis dan pengobatan yang tepat bagi Anda. Dosis Xeloda didasarkan pada luas permukaan tubuh Anda. Ini dapat dihitung dari berat dan tinggi badan Anda. Dosis normal untuk orang dewasa adalah 1250 mg/m^2 dari luas permukaan tubuh, diberikan dua kali sehari (pagi dan malam). Berikut ini diberikan dua contoh: Seseorang yang berat badannya 64 kg dan tingginya 1,64 m memiliki luas permukaan tubuh 1,7 m^2 dan harus meminum 4 tablet 500 mg. Seseorang yang berat badannya 80 kg dan tinggi badan 1,80 m memiliki luas permukaan tubuh 2,00 m^2 dan harus meminum 5 tablet 500 mg dua kali sehari.

Dokter Anda akan memberi tahu dosis yang perlu Anda minum, waktu untuk meminumnya dan berapa lama Anda harus meminumnya.
- Minum tablet pada **pagi dan malam hari** seperti yang diresepkan dokter Anda.
- Minum tablet dalam waktu **30 menit setelah makan berakhir** (sarapan dan makan malam) dan **telanlah secara keseluruhan dengan air putih, jangan digerus atau dibelah.**
- Penting agar Anda meminum semua obat seperti yang diresepkan oleh dokter Anda.

Tablet Xeloda biasanya diberikan selama 14 hari, diikuti dengan 7 hari periode istirahat (ketika tidak diberikan tablet). Periode 21 hari ini disebut sebagai satu siklus pengobatan.

Ketika dikombinasikan dengan obat lain, dosis normal untuk orang dewasa dapat menjadi lebih rendah dari 1250 mg/m^2 dari luas permukaan tubuh, dan mungkin Anda harus meminum tablet dalam periode waktu yang berbeda (misal setiap hari, tanpa periode istirahat).

Jika Anda meminum lebih banyak Xeloda dari yang seharusnya
Jika Anda meminum Xeloda lebih banyak dari yang seharusnya, hubungi dokter Anda secepat mungkin sebelum meminum dosis selanjutnya.
Anda mungkin akan mengalami efek samping jika Anda meminum *capecitabine* lebih banyak dari yang seharusnya: merasa atau menjadi sakit, diare, peradangan atau ulkus usus atau mulut, nyeri atau pendarahan dari usus atau perut, atau depresi sumsum tulang (berkurangnya jenis sel darah tertentu). Beri tahu dokter Anda segera jika Anda mengalami salah satu gejala ini.

Jika Anda lupa meminum Xeloda
Jangan meminum dosis yang terlupakan sama sekali. Jangan meminum dosis ganda untuk menggantikan dosis yang terlupakan. Namun, lanjutkan jadwal dosis rutin Anda dan cek ke dokter Anda.

Jika Anda berhenti meminum Xeloda
Tidak ada efek samping yang diakibatkan oleh penghentian pengobatan dengan *capecitabine*. Jika Anda menggunakan antikoagulan kumarin (misalnya mengandung *phenprocoumon*), penghentian *capecitabine* mungkin akan mengharuskan dokter Anda menyesuaikan dosis antikoagulan.
Jika ada pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter, perawat atau apoteker Anda.

4. Kemungkinan efek samping
Seperti semua obat, obat ini dapat menyebabkan efek samping, meskipun tidak terjadi pada setiap orang.

Segera **BERHENTI** meminum Xeloda dan hubungi dokter Anda jika terjadi salah satu gejala ini:
- ***Diare***: jika terjadi peningkatan 4 kali buang air besar (BAB) atau lebih dibandingkan dengan BAB normal Anda setiap hari atau diare pada malam hari.
- ***Muntah:*** jika Anda muntah lebih dari sekali dalam 24 jam.
- ***Mual:*** jika Anda kehilangan selera makan, dan jumlah makanan yang Anda makan setiap hari berkurang daripada biasanya.
- ***Seriawan:*** jika Anda mengalami nyeri, kemerahan, bengkak atau ulkus di dalam mulut dan/atau tenggorokan.
- ***Reaksi kulit pada tangan dan kaki:*** jika Anda mengalami nyeri, bengkak, kemerahan atau rasa kesemutan pada tangan dan/atau kaki.
- ***Demam:*** jika suhu badan Anda 38°C atau lebih.
- ***Infeksi:*** jika Anda mengalami tanda-tanda infeksi yang diakibatkan oleh bakteri atau virus, atau organisme lain.
- ***Nyeri dada:*** jika Anda mengalami nyeri yang terbatas pada pusat dada, khususnya jika terjadi saat olahraga.
- ***Sindrom Stevens-Johnson:*** jika Anda mengalami ruam merah atau ungu yang menyakitkan/nyeri yang menyebar dan melepuh dan/atau lesi lain mulai nampak pada membran

mukosa (misalnya mulut dan bibir), khususnya jika sebelumnya Anda pernah mengalami sensitivitas ringan, infeksi sistem pernafasan (misalnya bronkitis) dan/atau demam.

- ***Defisiensi DPD:*** jika Anda mengalami defisiensi DPD yang diketahui, maka Anda berisiko lebih tinggi mengalami toksisitas akut dini dan reaksi parah, membahayakan jiwa, atau fatal yang disebabkan oleh Xeloda (misalnya seriawan, peradangan mukosa, diare, neutropenia, dan neurotoksisitas).
- ***Angioedema:*** jika Anda mengalami gejala seperti pembengkakan terutama pada wajah, bibir, lidah atau tenggorokan yang membuat sulit menelan atau bernapas, gatal dan ruam, maka segera konsultasikan dengan dokter. Hal ini bisa menjadi tanda angioedema dan Anda mungkin memerlukan perawatan medis segera.

Jika terdeteksi dini, efek samping ini biasanya membaik dalam waktu 2 hingga 3 hari sejak berhentinya pengobatan. Namun, jika efek samping berlanjut, segera hubungi dokter Anda. Dokter Anda dapat menginstruksikan Anda untuk mengulangi pengobatan dengan dosis yang lebih rendah.
Reaksi kulit pada tangan dan kaki dapat mengarah pada hilangnya sidik jari, yang dapat memengaruhi identifikasi pada *scan* sidik jari.
Selain hal-hal di atas, jika Xeloda digunakan sendiri, efek samping yang sangat umum terjadi, yang mungkin memengaruhi lebih dari 1 dari 10 pasien adalah:

- nyeri perut
- ruam, kulit kering atau gatal
- kelelahan
- nafsu makan hilang (anoreksia)

Efek samping ini dapat menjadi lebih berat; oleh karena itu, penting agar Anda **selalu segera menghubungi dokter Anda** jika Anda mulai mengalami efek samping. Dokter Anda dapat menginstruksikan Anda untuk mengurangi dosis dan/atau untuk sementara menghentikan pengobatan dengan Xeloda. Hal ini akan membantu mengurangi kemungkinan efek samping terus berlanjut atau menjadi parah.

Efek samping lain adalah sebagai berikut:
Efek samping yang umum terjadi (dapat terjadi pada hingga 1 dari 10 pasien) termasuk:

- berkurangnya jumlah sel darah putih atau sel darah merah (ditunjukkan oleh pengujian)
- dehidrasi, kehilangan berat badan
- kurang tidur (insomnia), depresi
- sakit kepala, mengantuk, pusing, sensasi abnormal pada kulit (sensasi mati rasa atau rasa kesemutan), perubahan indra pengecap
- iritasi mata, peningkatan air mata, mata kemerahan (konjungtivitis)
- peradangan vena (tromboflebitis)
- nafas pendek, mimisan, batuk, pilek (*runny nose*)
- luka dingin atau infeksi herpes lain
- infeksi paru-paru atau sistem pernafasan (misalnya pneumonia atau bronkitis)
- perdarahan dari usus, konstipasi, sakit pada perut bagian atas, gangguan pencernaan, perut kembung, mulut kering
- ruam kulit, rambut rontok (alopesia), kulit memerah, kulit kering, gatal (pruritus), perubahan warna kulit, kulit mengelupas, peradangan kulit, kelainan kuku
- nyeri pada sendi, atau pada anggota badan (ekstrimitas), dada atau punggung

- demam, bengkak pada anggota badan, merasa sakit
- gangguan pada fungsi hati (ditunjukkan oleh pengujian darah) dan peningkatan bilirubin darah (diekskresi oleh hati)

Efek samping yang tidak biasa terjadi (dapat terjadi pada hingga 1 dari 100 pasien) termasuk:
- infeksi darah, infeksi saluran kemih, infeksi kulit, infeksi hidung dan tenggorokan, infeksi jamur (termasuk pada mulut), influenza, gastroenteritis, abses gigi
- benjolan di bawah kulit (lipoma)
- penurunan sel darah termasuk platelet, pengenceran darah (ditunjukkan oleh pengujian)
- alergi
- diabetes, penurunan kalium dalam darah, malnutrisi, peningkatan trigliserida darah
- kebingungan, serangan panik, depresi, penurunan libido
- kesulitan berbicara, gangguan daya ingat, kehilangan koordinasi gerakan, gangguan keseimbangan, pingsan, kerusakan saraf (neuropati) dan gangguan pada sensasi
- penglihatan kabur atau ganda
- vertigo, sakit telinga
- denyut jantung tidak teratur dan palpitasi (aritmia), nyeri dada dan serangan jantung (infark)
- bekuan darah pada vena dalam (*deep vein*), tekanan darah tinggi atau rendah, rasa panas di seluruh tubuh, dingin pada ekstremitas, bintik ungu pada kulit
- bekuan darah pada vena di paru-paru (emboli paru), gagal paru-paru, batuk darah, asma, napas pendek saat aktivitas
- obstruksi usus, pengumpulan cairan di perut, peradangan usus kecil atau besar, lambung atau kerongkongan, nyeri pada perut bagian bawah, gangguan pada perut, nyeri lambung (refluks makanan dari perut), darah pada tinja
- ikterus (kulit dan mata berwarna kuning)
- ulkus dan lepuh kulit, reaksi kulit terhadap cahaya matahari, telapak tangan kemerahan, bengkak atau sakit pada wajah
- bengkak atau kaku pada sendi, nyeri tulang, otot lemah atau kaku
- pengumpulan cairan pada ginjal, meningkatnya frekuensi buang air kecil di malam hari, inkontinensia, darah dalam urin, peningkatan kreatinin darah (tanda disfungsi ginjal)
- perdarahan abnormal dari vagina
- bengkak (edema), meriang dan menggigil

Beberapa dari efek samping ini lebih umum terjadi saat *capecitabine* digunakan bersama dengan obat lain untuk pengobatan kanker. Efek samping lain yang nampak dalam keadaan ini adalah sebagai berikut:

Efek samping umum terjadi (dapat terjadi pada hingga 1 dari 10 pasien) termasuk:
- penurunan natrium, magnesium atau kalsium darah, peningkatan gula darah
- nyeri saraf
- bunyi berdering atau berdengung di dalam telinga (*tinnitus*), kehilangan pendengaran
- peradangan vena
- cegukan, perubahan suara
- nyeri atau sensasi berubah/abnormal pada mulut, sakit pada rahang
- berkeringat, keringat di malam hari
- kram otot
- kesulitan berkemih, darah atau protein dalam urin

- lebam atau reaksi pada lokasi injeksi (diakibatkan oleh obat yang diberikan dengan injeksi pada saat yang sama)

Efek samping yang jarang terjadi (dapat terjadi pada hingga 1 dari 1.000 pasien) termasuk:
- penyempitan atau penyumbatan saluran air mata (stenosis duktus lakrimal)
- gagal hati
- peradangan yang menyebabkan disfungsi atau obstruksi sekresi empedu (hepatitis kolestasis)
- perubahan spesifik pada elektrokardiogram (perpanjangan QT)
- jenis aritmia tertentu (termasuk fibrilasi ventrikel, *torsade de pointes*, dan bradikardia)
- peradangan mata yang menyebabkan nyeri mata dan kemungkinan gangguan mata
- peradangan kulit yang menyebabkan bercak bersisik merah karena gangguan sistem imun

Efek samping yang sangat jarang terjadi (dapat terjadi pada hingga 1 dari 10.000 pasien) termasuk:
- reaksi kulit parah seperti ruam kulit, ulserasi dan melepuh yang dapat melibatkan ulkus mulut, hidung, genitalia, tangan, kaki dan mata (mata merah dan bengkak)

Pelaporan efek samping
Apabila Anda mengalami efek samping apapun, hubungi dokter, apoteker atau perawat Anda. Hal ini termasuk semua efek samping lainnya yang tidak tercantum dalam brosur ini. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi tambahan terkait keamanan obat ini.

Anda juga dapat melaporkan efek samping secara langsung melalui:

Pusat Farmakovogilans
c.q. Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif

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5. Bagaimana cara penyimpanan Xeloda
- Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
- Simpan di bawah suhu 30°C.
- Jangan menggunakan obat ini setelah tanggal kedaluwarsa yang tertera pada dus dan blister setelah kata 'EXP'. Tanggal kedaluwarsa tersebut merujuk pada tanggal terakhir dari bulan yang disebutkan.
- Jangan membuang obat melalui pembuangan air limbah atau limbah rumah tangga. Tanyakan kepada apoteker Anda cara membuang obat yang tidak lagi Anda gunakan. Tindakan ini akan membantu melindungi lingkungan.

6. Isi kemasan dan informasi lain
Apa isi Xeloda
Zat aktifnya adalah *capecitabine* (500 mg per tablet salut selaput).
Bahan tambahan lainnya adalah:

- Inti tablet: laktosa anhidrat, natrium *croscarmellose*, *hypromellose*, *microcrystalline cellulose*, magnesium stearat.
- Salut tablet: *hypromellose*, titanium dioksida, oksida besi kuning dan merah, talk.

Seperti apakah Xeloda dan isi dari kemasannya

Tablet bikonveks bersalut selaput berwarna *peach*, berbentuk lonjong dengan penanda '500' pada satu sisi dan 'Xeloda' pada sisi lainnya.

Setiap kemasan berisi 120 tablet salut selaput (12 blister masing-masing 10 tablet salut selaput).

Obat: Jauhkan dari jangkauan dan pandangan anak-anak
Harus dengan resep dokter

Kemasan yang terdaftar

Tablet salut selaput 500 mg
Dus, 12 blister @ 10 tablet salut selaput No. Reg.: DKI2157510817A1

Dibuat oleh:

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