

Data Sheet

Xeloda[®]

Capecitabine tablets 150 mg and 500 mg

Cytostatic agent

Pharmaceutical Form

Film-coated tablets 150 mg and 500 mg.

Qualitative and Quantitative Composition

Active ingredient

Capecitabine.

Excipients

Anhydrous lactose, croscarmellose sodium, hypromellose, microcrystalline cellulose, magnesium stearate, titanium dioxide, talc, yellow and red iron oxide.

Appearance

Xeloda 150 mg film-coated tablets are light peach in colour, biconvex/oblong in shape with Xeloda engraved on one face and 150 engraved on the reverse.

Xeloda 500 mg film-coated tablets are peach in colour, biconvex/oblong in shape with Xeloda engraved on one face and 500 on the reverse.

Clinical Particulars

Therapeutic Indications

Breast cancer

Xeloda is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen unless therapy with these and other standard agents are clinically contraindicated.

Xeloda in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline containing chemotherapy

Colon cancer

Xeloda is indicated for the adjuvant treatment of patients with Dukes' Stage C and high-risk Stage B colon cancer, either as monotherapy or in combination with oxaliplatin.

Colorectal cancer

Xeloda is indicated for first-line treatment of patients with metastatic colorectal cancer.

Oesophagogastric Cancer

Xeloda is indicated for the first-line treatment of patients with advanced oesophagogastric cancer in combination with a platinum-based regimen.

Dosage and Administration

Standard dosage

Xeloda tablets should be swallowed with water within 30 minutes after a meal.

Monotherapy

Colon, colorectal and breast cancer

The recommended monotherapy starting dose of Xeloda is 1250 mg/m² administered twice daily (morning and evening; equivalent to 2500 mg/m² total daily dose) for 14 days followed by a 7-day rest period.

Combination therapy

Breast cancer

In combination with docetaxel, the recommended starting dose of Xeloda is 1250 mg/m² twice daily for 14 days followed by a 7-day rest period, combined with docetaxel at 75 mg/m² as a 1-hour intravenous infusion every 21 days.

Pre-medication according to the docetaxel labelling should be started prior to docetaxel administration for patients receiving the Xeloda plus docetaxel combination.

Colorectal cancer

In combination with oxaliplatin with or without bevacizumab the recommended starting dose of Xeloda is 1000 mg/m² 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 week cycle, on day 1 every 3 weeks bevacizumab is administered as a 7.5 mg/kg intravenous infusion over 30 to 90 minutes followed by oxaliplatin administered as a 130 mg/m² intravenous infusion over 2 hours.

Colon cancer

In combination with oxaliplatin the recommended starting dose of Xeloda is 1000 mg/m² 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 week cycle, on day 1 oxaliplatin is administered as a 130 mg/m² intravenous infusion over 2 hours.

Oesophagogastric cancer

In triplet combination with epirubicin and cisplatin/oxaliplatin for oesophagogastric cancer, the recommended starting dose of Xeloda is 625 mg/m² twice daily as a continuous regimen. Epirubicin is administered as a 50 mg/m² intravenous bolus on day 1 of a 3 week cycle. Platinum therapy should consist of either cisplatin administered at a dose of 60 mg/m² given as a 2 hour intravenous infusion on day 1 of a 3 week cycle; or oxaliplatin administered at a dose of 130 mg/m² given as a 2 hour intravenous infusion on day 1 of a 3 week cycle.

In combination with cisplatin (doublet) with or without trastuzumab for gastric cancer, the recommended starting dose of Xeloda is 1000 mg/m² 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. Cisplatin is administered at a dose of 80 mg/m² as a 2 hour intravenous infusion on day 1 of a 3-week cycle.

Premedication to maintain adequate hydration and anti-emesis according to the cisplatin and oxaliplatin product information should be started prior to cisplatin/oxaliplatin administration for patients receiving Xeloda in combination with these agents.

Xeloda dose is calculated according to body surface area. Tables 1 and 2 show examples of the standard and reduced dose calculations (see Dosage adjustments during treatment) for a starting dose of Xeloda of either 1250 mg/m² or 1000 mg/m².

Table 1: Standard and reduced dose calculations according to body surface area for a starting dose of Xeloda of 1250 mg/m²

	Dose level 1250 mg/m ² (twice daily)				
	Full dose 1250 mg/m ² (twice daily)	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 (twice daily)	Reduced dose (50%) 625 mg/m ² (twice daily)
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/m²

	Dose level 1000 mg/m ² (twice daily)				
	Full dose 1000 mg/m ² (twice daily)	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 (twice daily)	Reduced dose (50%) 500 mg/m ² (twice daily)
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, treatment can be continued at the same dose without reduction or interruption.

Dosage modifications are not recommended for Grade 1 events. Therapy with Xeloda should be interrupted if a Grade 2 or 3 adverse experience occurs. Once the adverse event has resolved or decreased in intensity to Grade 1, Xeloda therapy may be restarted at full dose or as adjusted according to Table 4. If a Grade 4 experience occurs, therapy should be discontinued or interrupted until the experience has resolved or decreased to Grade 1, and therapy can then 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. For examples of toxicity grades for some relevant adverse events, please refer to Table 3.

Table 3: Toxicity Grades for Some Relevant Adverse Events

Intensity of Clinical Adverse Events*				
Adverse Events	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life-threatening (Grade 4)
Diarrhoea	Increase of 1 - 3 stools/day	Increase of 4 - 6 stools/day, or nocturnal stools	Increase of 7 - 9 stools/day or incontinence and malabsorption	Increase of ≥ 10 stools/day or grossly bloody diarrhoea or the need for parenteral support
Nausea	No significant effect on food intake	Food intake significantly decreased but able to eat intermittently	Unable to eat	
Vomiting	1 episode in a 24-hour period	2 - 5 episodes in a 24-hour period	6 - 10 episodes in a 24-hour period	> 10 episodes in a 24-hour period or the need for parenteral support
Hand-foot syndrome ^{**} (clinical domain)	Numbness, tingling, painless erythema, and swelling	Painful erythema and swelling	Moist desquamation, ulceration, blistering, and severe pain	
Hand-foot syndrome ^{**} (functional domain)	Discomfort which does not disrupt normal activities	Discomfort which affects activities of daily living	Severe discomfort, unable to work or perform activities of daily living	
Stomatitis	Erythema without pain	Painful erythema, oedema, or ulcers, but able to eat	Painful erythema restricting ability to eat	

* The intensity of clinical adverse events was graded on a 4-point scale following the National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC).

** Criteria as established by Roche protocol.

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.

The following table shows the recommended dose modifications following toxicity with Xeloda:

Table 4: Xeloda dose reduction schedule

Toxicity NCIC grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle (% of starting dose)
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1 st appearance	Interrupt until resolved to Grade 0 - 1	100%
2 nd appearance	Interrupt until resolved to Grade 0 - 1	75%
3 rd appearance	Interrupt until resolved to Grade 0 - 1	50%
4 th appearance	Discontinue treatment permanently	Not applicable
Grade 3		
1 st appearance	Interrupt until resolved to Grade 0 - 1	75%
2 nd appearance	Interrupt until resolved to Grade 0 - 1	50%
3 rd appearance	Discontinue treatment permanently	Not applicable
Grade 4		

1 st 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%
2 nd appearance	Discontinue permanently	Not applicable

*According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. For hand-foot syndrome and hyperbilirubinaemia, see Warnings and Precautions.

General combination therapy

Dose modification for toxicity when Xeloda is used in combination with other therapies should be made according to Table 4 for Xeloda and according to the appropriate Prescribing Information 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 medicines 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 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.

Special dosage instructions

Patients with hepatic impairment due to liver metastases

In patients with mild to moderate hepatic impairment due to liver metastases, no starting dose adjustment is necessary. However, such patients should be carefully monitored (see Pharmacokinetic Properties and Warnings and Precautions). Patients with severe hepatic impairment have not been studied.

Patients with renal impairment

In patients with moderate renal impairment (creatinine clearance 30 – 50 mL/min [Cockcroft and Gault]) at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m² is recommended. In patients with mild renal impairment (creatinine clearance 51 - 80 mL/min) no adjustment in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3, or 4 adverse event with subsequent dose adjustment as outlined in Table 4 above (see Pharmacokinetics in special populations). If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, Xeloda should be discontinued. The dose adjustment recommendations for patients with moderate renal impairment apply both to monotherapy and combination use. For dosage calculations, see Tables 1 and 2.

Children

The safety and efficacy of Xeloda in children have not been established.

Elderly

For Xeloda monotherapy, no adjustment of the starting dose is needed. However, severe Grade 3 or 4 treatment-related adverse events were more frequent in patients over 80 years of age compared to

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

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. 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/m² twice daily) is recommended. For dosage calculations, see Table 2.

In combination with irinotecan: for patients 65 years of age or more, a starting dose reduction of Xeloda to 800mg/m² twice daily is recommended.

Contraindications

Xeloda is contraindicated in patients with known hypersensitivity to capecitabine or to any of its components.

Xeloda is contraindicated in patients who have a history of severe and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil.

As with other fluoropyrimidines, Xeloda is contraindicated in patients with known dihydropyrimidine dehydrogenase (DPD) deficiency.

Xeloda should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine (see 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).

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

Warnings and Precautions

Warnings

Diarrhoea

Xeloda can induce diarrhoea, which can sometimes be severe. Patients with severe diarrhoea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. Standard anti-diarrhoea treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Dose reduction should be applied as necessary (see Dosage and Administration).

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 should be applied for the precipitating adverse event as necessary (see Dosage and Administration).

Precautions

The spectrum of cardiotoxicity observed with Xeloda is similar to that of other fluorinated pyrimidines. This includes myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure and electrocardiographic changes. These adverse events may be more common in patients with a prior history of coronary artery disease.

Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhoea, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. A link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-FU therefore cannot be excluded.

Xeloda can induce hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema), which is a cutaneous toxicity. For patients receiving Xeloda monotherapy in the metastatic setting, the median time to onset of 79 days, range from 11 to 360 days), with a severity range of Grades 1 to 3.

Grade 1 hand-foot syndrome is defined by numbness, dysaesthesia/paraesthesia, tingling, or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 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 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 Dosage and Administration). When Xeloda and cisplatin are used in combination, the use of vitamin B6 (pyridoxine) is not advised for symptomatic or secondary prophylactic treatment of hand-foot syndrome, because of published reports that it may decrease the efficacy of cisplatin.

Xeloda can induce hyperbilirubinaemia. Administration of Xeloda should be interrupted if treatment-related elevations in bilirubin of $> 3.0 \times \text{ULN}$ or treatment-related elevations in hepatic aminotransferases (ALT, AST) of $> 2.5 \times \text{ULN}$ occur. Treatment may be resumed when bilirubin decreases to $\leq 3.0 \times \text{ULN}$ or hepatic aminotransferases decrease to $\leq 2.5 \times \text{ULN}$.

In a medicine 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. 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 (see Interactions with other Medicinal Products and other Forms of Interaction).

General

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

Interactions with other Medicinal Products and other Forms of Interaction

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. 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 P-450 2C9 substrates

No formal interaction studies with capecitabine and other medicines known to be metabolised by the cytochrome P450 2C9 isoenzyme have been conducted. Care should be exercised when Xeloda is co-administered with these medicines.

Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of Xeloda with phenytoin. Formal 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.

Medicine-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.

Antacid

The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of capecitabine 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)

The effect of leucovorin on the pharmacokinetics of Xeloda was investigated in cancer patients. Leucovorin has no effect on the pharmacokinetics of capecitabine and its metabolites. However, leucovorin has an effect on the pharmacodynamics of Xeloda and its toxicity may be enhanced by leucovorin.

Sorivudine and analogues

A clinically significant 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 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 the 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.

Use in Special Populations

Pregnancy

Pregnancy Category D

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 foetal harm if administered to pregnant women. In reproductive toxicity studies in animals, capecitabine administration caused embryoletality 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. If Xeloda is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, the patient must be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Xeloda.

Nursing mothers

It is not known whether capecitabine is secreted in human milk. In a study of single oral administration of Xeloda to lactating mice, a significant amount of capecitabine metabolites was detected in the milk. Nursing should be discontinued during Xeloda treatment.

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 adverse events, such as diarrhoea, nausea and vomiting (see Special dosage instructions). When Xeloda was used in combination with other agents elderly patients (≥ 65 years) experienced more Grade 3 and Grade 4 adverse reactions and adverse reactions 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 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.

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 adverse events was higher in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) (see Special dosage instructions).

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 Pharmacokinetics in special populations and Special dosage instructions).

Undesirable Effects

Clinical trials

Adverse reactions 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 different chemotherapy regimens for multiple indications. Adverse reactions are added to the appropriate category in the tables below according to the highest incidence from the pooled analysis of seven clinical trials. Within each frequency grouping, adverse reactions are listed in descending order of seriousness. Frequencies are defined as very common $\geq 1/10$, common $\geq 5/100$ to $< 1/10$ and uncommon $\geq 1/1000$ to $< 1/100$.

Xeloda monotherapy

Safety data of Xeloda monotherapy were reported for patients who received adjuvant treatment for colon cancer and for patients who received treatment for metastatic breast cancer or metastatic colorectal cancer. The safety information includes data from a phase III trial in adjuvant colon cancer (995 patients treated with Xeloda and 974 treated with IV 5-FU/LV) and from 4 phase II trials in female patients with breast cancer ($n = 319$) and 3 trials (1 phase I and 2 phase III trials) in male and female patients with colorectal cancer ($n = 630$). The safety profile of Xeloda monotherapy is comparable in patients who received adjuvant treatment for colon cancer and in those who received treatment for metastatic breast cancer or metastatic colorectal cancer. The intensity of adverse reactions were graded according to the toxicity categories of the NCIC CTC Grading System.

Table 5: Summary of adverse reactions reported in $\geq 5\%$ of patients treated with Xeloda monotherapy

Body System ADR	Very Common ($\geq 10\%$)	Common ($\geq 5\% - < 10\%$)
Metabolism and nutrition disorders	Anorexia (G3/4:1%)	Dehydration (G3/4: 3%) Appetite decreased (G3/4:<1%)
Nervous system disorders		Paraesthesia Dysgeusia (G3/4:<1%) Headache (G3/4:<1%) Dizziness (excl. vertigo) (G3/4:<1%)
Eye disorders		Lacrimation increased Conjunctivitis (G3/4:<1%)
Gastrointestinal disorders	Diarrhoea (G3/4: 13%) Vomiting (G3/4: 4%) Nausea (G3/4: 4%)	Constipation (G3/4:<1%) Abdominal pain upper (G3/4:<1%)

	Stomatitis (all)* (G3/4: 4%) Abdominal pain (G3/4: 3%)	Dyspepsia (G3/4:<1%)
Hepatobiliary disorders		Hyperbilirubinaemia (G3/4:1%)
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome (G3/4: 17%) Dermatitis (G3/4:<1%)	Rash Alopecia Erythema (G3/4:1%) Dry Skin (G3/4:<1%)
General disorders and administration site conditions	Fatigue (G3/4: 3%) Lethargy (G3/4:<1%)	Pyrexia (G3/4:<1%) Weakness (G3/4:<1%) Asthenia (G3/4:<1%)

* stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration

Skin fissures were reported to be at least remotely related to Xeloda in less than 2% of the patients in seven completed clinical trials ($n = 949$).

The following adverse reactions represent known toxicities with fluoropyrimidine therapy and were reported to be at least remotely related to Xeloda in less than 5 % of patients in seven completed clinical trials ($n = 949$).

Gastrointestinal disorders: Dry mouth, flatulence, adverse reactions related to inflammation/ulceration of mucous membranes such as oesophagitis, gastritis, duodenitis, colitis, gastrointestinal haemorrhage

Cardiac disorders: Oedema lower limb, cardiac chest pain including angina, cardiomyopathy, myocardial ischemia/infarction, cardiac failure, sudden death, tachycardia, atrial arrhythmias including atrial fibrillation, and ventricular extrasystoles

Nervous system disorders: Taste disturbance, insomnia, confusion, encephalopathy, and cerebellar signs such as ataxia, dysarthria, impaired balance, abnormal coordination

Infections and infestations: Adverse reactions related to bone marrow depression, immune system compromise, and/or disruption of mucous membranes, such as local and fatal systemic infections (including bacterial, viral, fungal aetiologies) and sepsis

Blood and lymphatic system disorders: Anaemia, bone marrow depression, pancytopenia

Skin and subcutaneous tissue disorders: Pruritus, localised exfoliation, skin hyperpigmentation, nail disorders, photosensitivity reactions, radiation recall syndrome

General disorders and administration site conditions: asthenia, pain in limb, lethargy, chest pain (non-cardiac)

Eye: Eye irritation

Respiratory: Dyspnoea, cough

Musculoskeletal: Back pain, myalgia, arthralgia

Psychiatric disorders: Depression

Hepatic failure and cholestatic hepatitis have been reported during clinical trials and post-marketing exposure. A causal relationship with Xeloda treatment has not been established.

Xeloda in combination therapy

Table 6 lists adverse reactions associated with the use of Xeloda in combination therapy with different chemotherapy regimens in multiple indications and occurred in addition to those seen with monotherapy and/or at a higher frequency grouping. The safety profile was similar across all indications and combination regimens. These reactions occurred in $\geq 5\%$ of patients treated with Xeloda in combination with other chemotherapies. Adverse reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin, hypertension seen with bevacizumab); however, an exacerbation by Xeloda therapy cannot be excluded.

Table 6: Very common and common adverse reactions for Xeloda in combination with different chemotherapies in addition to those seen for Xeloda monotherapy

Body System Adverse Event	Very Common $\geq 10\%$	Common $\geq 5\%$ to $< 10\%$
Infections and Infestations		Infection ⁺ Oral candidiasis
Blood and lymphatic system disorders	Neutropenia ⁺ Leukopenia ⁺ Febrile neutropenia ⁺ Thrombocytopenia ⁺ Anaemia ⁺	
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia Weight decreased
Psychiatric disorders		Insomnia
Nervous system disorders	Neuropathy peripheral Peripheral sensory neuropathy Neuropathy Taste disturbance Paraesthesia Dysgeusia Dysaesthesia Headache	Hypoaesthesia
Eye disorders	Lacrimation increased	
Vascular Disorders	Thrombosis/embolism Hypertension Lower limb oedema	
Respiratory	Dysaesthesia pharynx Sore throat	Epistaxis Dysphonia rhinorrhoea Dyspnoea
Gastrointestinal disorders	Constipation Dyspepsia	Dry mouth
Skin and subcutaneous tissue	Alopecia	

disorders	Nail disorder	
Musculoskeletal and connective tissue disorders	Arthragia Myalgia Pain in extremity	Pain in jaw Back pain
General disorders and administration site conditions	Pyrexia Asthenia Weakness Temperature intolerance	Fever ⁺ Pain

Frequencies based on all grades except those denoted with ⁺, which are based on G3/4 Adverse reactions only.

Hypersensitivity reactions (2%) and cardiac ischaemia/infarction (3%) have been reported commonly for Xeloda in combination with other chemotherapy but in less than 5% of patients.

Rare or uncommon adverse reactions reported for Xeloda in combination with other chemotherapy are consistent with the adverse reactions reported for Xeloda monotherapy or the combination product monotherapy.

Laboratory Abnormalities

The following table displays laboratory abnormalities observed in 995 patients, regardless of relationship to treatment, with Xeloda in the adjuvant treatment of colon cancer.

Table 7: Laboratory abnormalities^a: Xeloda monotherapy in adjuvant colon cancer and in metastatic breast and colorectal cancer

Parameter ^a	Xeloda 1250 mg/m ² twice daily intermittent
	Patients with Grade 3 / 4 abnormality (%)
Increased ALAT (SGPT)	1.6
Increased ASAT (SGOT)	1.1
Increased alkaline phosphatase	3.5
Increased calcium	1.1
Decreased calcium	2.3
Decreased granulocytes	0.3
Decreased haemoglobin	3.1
Decreased lymphocytes	44.4
Decreased neutrophils	3.6
Decreased neutrophils/granulocytes	2.4
Decreased platelets	2.0
Decreased potassium	0.3
Increased serum creatinine	0.5
Decreased sodium	0.4
Increased bilirubin	20
Hyperglycaemia	4.4

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

Post-marketing experience

The following adverse reactions have been identified during post-marketing exposure:

Very rare: lacrimal duct stenosis NOS.

Very rare: hepatic failure and cholestatic hepatitis have been reported during clinical trials and post-marketing exposure.

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.

Pharmacological Properties and Effects

Pharmacodynamic Properties

Mechanism of action

Capecitabine is a fluoropyrimidine carbamate derivative, which was designed as an orally administered, tumour-activated and tumour-selective cytotoxic agent.

Capecitabine is non-cytotoxic *in vitro*. However, *in vivo*, it is sequentially converted to the cytotoxic moiety, 5-fluorouracil (5-FU), which is further metabolised.

Formation of 5-FU is catalysed preferentially at the tumour site by the tumour-associated angiogenic factor thymidine phosphorylase (dThdPase), thereby minimising the exposure of healthy tissues to systemic 5-FU.

The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations of 5-FU within tumour tissues. Following oral administration of capecitabine to patients with colorectal cancer ($n = 8$), the ratio of 5-FU concentration in colorectal tumours to adjacent tissues was 3.2 (range, 0.9 to 8.0). The ratio of 5-FU concentration in tumour to plasma was 21.4 (range, 3.9 to 59.9) whereas the ratio in healthy tissues to plasma was 8.9 (range, 3.0 to 25.8). Thymidine phosphorylase activity was four times greater in primary colorectal tumour than in adjacent normal tissue.

Several human tumours, such as breast, gastric, colorectal, cervical and ovarian cancers, have a higher level of thymidine phosphorylase (capable of converting 5'-DFUR [5'-deoxy-5-fluorouridine] to 5-FU) than corresponding normal tissues.

Normal and tumour cells metabolise 5-FU to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor N⁵⁻¹⁰-methylene tetrahydrofolate bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from uracil. Thymidylate is the necessary precursor of thymidine triphosphate, which is essential for the synthesis of DNA, so that a deficiency of this compound can inhibit cell division. Second, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate (UTP) during the synthesis of RNA. This metabolic error can interfere with RNA processing and protein synthesis.

Clinical/efficacy studies

Colon and Colorectal cancer

Monotherapy - adjuvant colon cancer

Data from one multicentre, randomised, controlled phase 3 clinical trial in patients with Dukes Stage C colon cancer supports the use of Xeloda for the adjuvant treatment of patients with colon cancer (XACT Study: M66001). In this trial, 1987 patients were randomised to treatment with Xeloda (1250 mg/m² 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/m² leucovorin IV followed by 425 mg/m² 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 (DFS) ($p = 0.0001$, non-inferiority margin 1.2). In the all-randomised population, tests for difference of Xeloda vs. 5-FU/LV in DFS and overall survival (OS) showed hazard ratios of 0.88 (95% CI 0.77 – 1.01; $p = 0.068$) and 0.86 (95% CI 0.74 – 1.01; $p = 0.060$), respectively. The median follow up at the time of the analysis was 6.9 years.

Study M66001 did not include patients with Dukes Stage B disease, however, the findings of the study are considered to support the use of XELODA as adjuvant therapy in patients with high-risk stage B disease, such as those with inadequately sampled nodes, T4 lesions, perforation or poorly differentiated histology.

Combination therapy - adjuvant colon cancer

Data from a multicentre, randomised, controlled phase III clinical trial in patients with Dukes' Stage C colon cancer supports the use of Xeloda in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer (NO16968). In this trial, 944 patients were randomised to 3 week cycles for 24 weeks with Xeloda (1000 mg/m² twice daily for 2 weeks followed by a 7-day rest period) in combination with oxaliplatin (130 mg/m² intravenous infusion over 2 hours on day 1 every 3 weeks); 942 patients were randomised to bolus 5-FU and leucovorin. In the primary analysis (ITT population), median observation time was 57 months for DFS and 59 months for OS. XELOX was shown to be significantly superior to 5-FU/LV (HR = 0.80 [95% CI: 0.69; 0.93]; $p = 0.0045$). The 3 year DFS rate was 71% for XELOX versus 67% for 5-FU/LV. The analysis for the secondary endpoint of relapse free survival (RFS) supports these results with a HR of 0.78 ([95% CI: 0.67; 0.92]; $p = 0.0024$) for XELOX vs. 5-FU/LV. XELOX showed a trend towards superior OS with a HR of 0.87 ([95% CI: 0.72; 1.05]; $p = 0.1486$). The 5 year OS rate was 78% for XELOX versus 74% for 5-FU/LV.

Monotherapy – metastatic colorectal cancer

Data from two identically designed, multicentre, randomised, controlled phase 3 clinical trials support the use of Xeloda for first-line treatment of metastatic colorectal cancer (SO14695; SO14796). In these trials, 603 patients were randomised to treatment with Xeloda (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period and given as 3-week cycles) and 604 patients were randomised to treatment with 5-FU and leucovorin (Mayo regimen: 20 mg/m² leucovorin IV followed by 425 mg/m² IV bolus 5-FU, on days 1 to 5, every 28 days).

The overall objective response rates in the all-randomised 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).

Combination therapy – first-line treatment of colorectal cancer

Data from a multicentre, randomised, controlled phase III clinical study (N016966) support the use of Xeloda in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab (BV) for the first-line treatment of metastatic colorectal cancer. The study contained two parts: an initial 2-arm part in which patients were randomised to two different treatment groups, including XELOX or FOLFOX-4, and a subsequent 2 x 2 factorial part with four different treatment groups, including XELOX + placebo (P), FOLFOX-4+P, XELOX+BV, and FOLFOX-4+BV. The treatment regimens are summarised in the table below.

Table 8: Treatment regimens in Study NO16966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + Avastin	Oxaliplatin	85 mg/m ² IV 2 hr	Oxaliplatin on day 1, every 2 weeks
	Leucovorin	200 mg/m ² IV 2 hr	Leucovorin on days 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m ² IV bolus, 600 mg/ m ² IV 22 hr	5-fluorouracil IV bolus/infusion, each on days 1 and 2 , every 2 weeks
	Placebo or Avastin	5 mg/kg IV 30-90 m	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ Avastin	Oxaliplatin	130 mg/m ² IV 2 hr	Oxaliplatin on day 1, every 3 weeks
	Capecitabine	1000 mg/m ² oral bd	Capecitabine oral bd for 2 weeks (followed by 1 week off treatment)
	Placebo or Avastin	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, every 3 weeks
5-Fluorouracil: IV bolus injection immediately after leucovorin			

Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival in the eligible patient population and the intent-to-treat population (see table 9 below). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival. A comparison of XELOX plus bevacizumab versus FOLFOX-4 plus bevacizumab was a pre-specified exploratory analysis. In this treatment subgroup comparison, XELOX plus bevacizumab was similar compared to FOLFOX-4 plus bevacizumab in terms of progression-free survival (hazard ratio 1.01 [97.5% CI 0.84, 1.22]). The median follow up at the time of the primary analyses in the intent-to-treat population was 1.5 years; data from analyses following an additional 1 year of follow up are also included in the table below.

Table 9: Key non-inferiority results for the primary analysis and 1-year follow-up data (EPP and ITT populations, Study NO16966)

PRIMARY ANALYSIS		
	XELOX/XELOX+P/ XELOX+BV (EPP*: n = 967; ITT**: n = 1017)	FOLFOX-4/FOLFOX-4+P/ FOLFOX-4+BV (EPP*: n = 937; ITT**: n = 1017)
Population	Median Time to Event (Days)	
	HR (97.5% CI)	
Parameter: Progression-free Survival		

EPP	241	259	1.05 (0.94; 1.18)
ITT	244	259	1.04 (0.93; 1.16)
Parameter: Overall Survival			
EPP	577	549	0.97 (0.84; 1.14)
ITT	581	553	0.96 (0.83; 1.12)
ADDITIONAL 1 YEAR OF FOLLOW UP			
Population	Median Time to Event (Days)		HR(97.5% CI)
Parameter: Progression-free Survival			
EPP	242	259	1.02 (0.92; 1.14)
ITT	244	259	1.01 (0.91; 1.12)
Parameter: Overall Survival			
EPP	600	594	1.00 (0.88; 1.13)
ITT	602	596	0.99 (0.88; 1.12)

*EPP=eligible patient population; **ITT=intent-to-treat population

Data from a randomised, controlled phase III study (CAIRO) support the use of Xeloda at a starting dose of 1000 mg/m² for 2 weeks every 3 weeks in combination with irinotecan for the first-line treatment of patients with metastatic colorectal cancer. The efficacy in terms of Overall Response Rate (ORR), Progression Free Survival (PFS) and Overall Survival (OS) was similar to that reported in pivotal studies of 5-FU, leucovorin, and irinotecan (FOLFIRI).

Data from an interim analysis of a multicentre, randomised, controlled phase II study (AIO KRK 0604) support the use of Xeloda at a starting dose of 800 mg/m² for 2 weeks every 3 weeks in combination with irinotecan and bevacizumab for the first-line treatment of patients with metastatic colorectal cancer. In this study, 115 patients were randomised to treatment with Xeloda combined with irinotecan (XELIRI) and bevacizumab: Xeloda (800 mg/m² twice daily for two weeks followed by a 7-day rest period), irinotecan (200 mg/m² as a 30 minute infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks); a total of 118 patients were randomised to treatment with Xeloda combined with oxaliplatin plus bevacizumab: Xeloda (1000 mg/m² twice daily for two weeks followed by a 7-day rest period), oxaliplatin (130 mg/m² as a 2 hour infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/m² as a 30 to 90 minute infusion on day 1 every 3 weeks). Progression-free survival at 6 months in the intent-to-treat population was 80% (XELIRI plus bevacizumab) versus 74% (XELOX plus bevacizumab). Overall response rate (complete response plus partial response) was 47% (XELIRI plus bevacizumab) versus 45% (XELOX plus bevacizumab).

Combination therapy – Second-line treatment of colorectal cancer

Data from a multicentre, randomised, controlled phase III clinical study (NO16967) support the use of Xeloda in combination with oxaliplatin for the second-line treatment of metastatic 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 randomised to treatment with XELOX or FOLFOX-4. For the dosing schedule of XELOX and FOLFOX-4 (without addition of placebo or bevacizumab), refer to Table 8. XELOX was demonstrated to be non-inferior to FOLFOX-4 in terms of progression-free survival in the per-protocol population and intent-to-treat population (see table below). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival. 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 10: Key non-inferiority efficacy results for the primary analysis and 6-month follow-up data of Study NO16967 (PPP and ITT populations)

PRIMARY ANALYSIS			
	XELOX (PPP*: n = 251; ITT**: n = 313)	FOLFOX-4 (PPP*: n = 252; ITT**: n = 314)	
Population	Median Time to Event (Days)		HR (95% CI)
Parameter: Progression-free Survival			
PPP	154	168	1.03 (0.87; 1.24)
ITT	144	146	0.97 (0.83; 1.14)
Parameter: Overall Survival			
PPP	388	401	1.07 (0.88; 1.31)
ITT	363	382	1.03 (0.87; 1.23)
ADDITIONAL 6 MONTHS OF FOLLOW UP			
Population	Median Time to Event (Days)		HR (95% CI)
Parameter: Progression-free Survival			
PPP	154	166	1.04 (0.87; 1.24)
ITT	143	146	0.97 (0.83; 1.14)
Parameter: Overall Survival			
PPP	393	402	1.05 (0.88; 1.27)
ITT	363	382	1.02 (0.86; 1.21)

*PPP=per-protocol population; **ITT=intent-to-treat population

A pooled analysis of the efficacy data from first-line (study NO16966; initial 2-arm part) and second line treatment (study NO16967) further support the non-inferiority results of XELOX versus FOLFOX-4 as obtained in the individual studies: progression-free survival in the per-protocol population (hazard ratio 1.00 [95% CI: 0.88; 1.14]) with a median progression-free survival of 193 days (XELOX; 508 patients) versus 204 days (FOLFOX-4; 500 patients). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of overall survival (hazard ratio 1.01 [95% CI: 0.87; 1.17]) with a median overall survival of 468 days (XELOX) versus 478 days (FOLFOX-4).

Combination therapy - Gastric cancer

Data from a multicentre, randomised, controlled phase 3 clinical trial in patients with advanced or metastatic gastric cancer supports the use of Xeloda for the treatment of advanced gastric cancer. In this trial, 160 patients were randomised to treatment with Xeloda (1000 mg/m² twice daily for 2 weeks followed by a 7-day rest period) and cisplatin (80 mg/m² as a 2-hour infusion every 3 weeks). A total of 156 patients were randomised to treatment with 5-FU (800 mg/m² per day, continuous infusion on days 1 to 5 every 3 weeks) and cisplatin (80 mg/m² as a 2-hour infusion on day 1, every 3 weeks). The primary objective of the study was met, Xeloda in combination with cisplatin was at least equivalent to 5-FU in combination with cisplatin in terms of progression-free survival in the per-protocol analysis. The result for duration of survival (overall survival) was similar to the result for progression-free survival (Table 11).

Table 11: Summary of results for key efficacy parameters (PPP, Study ML17032)

Parameter	Median (Months) (95% CI)		Hazard Ratio (95% CI)*
	Xeloda/cisplatin (n = 139)	5-FU/cisplatin (n = 137)	
Progression-free survival	5.6 (4.9, 7.3)	5.0 (4.2, 6.3)	0.81 (0.63, 1.04)
Duration of survival	10.5 (9.3, 11.2)	9.3 (7.4, 10.6)	0.85 (0.64, 1.13)

*Unadjusted treatment effect in Cox proportional model.

Data from a randomised multicentre, phase III study comparing capecitabine to 5-FU and oxaliplatin to cisplatin in patients with advanced oesophagogastric cancer supports the use of Xeloda for the first-line treatment of advanced oesophagogastric cancer. In this trial, 1002 patients were randomised in a 2x2 factorial design to one of the following 4 arms:

- ECF: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m² as a two hour infusion on day 1 every 3 weeks) and 5-FU (200 mg/m² daily given by continuous infusion via a central line).
- ECX: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m² as a two hour infusion on day 1 every 3 weeks), and Xeloda (625 mg/m² twice daily continuously).
- EOF: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m² given as a 2 hour infusion on day 1 every three weeks), and 5-FU (200 mg/m² daily given by continuous infusion via a central line).
- EOX: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m² given as a 2 hour infusion on day 1 every three weeks), and Xeloda (625 mg/m² twice daily continuously).

The primary efficacy analyses in the per protocol population demonstrated non-inferiority in overall survival for capecitabine- vs. 5-FU-based regimens (hazard ratio 0.86, 95% CI: 0.8 to 0.99) and for oxaliplatin- vs. cisplatin-based regimens (hazard ratio 0.92, 95% CI: 0.8 to 1.1). The median overall survival was 10.9 months in capecitabine-based regimens and 9.6 months in 5-FU based regimens. The median overall survival was 10.0 months in cisplatin-based regimens and 10.4 months in oxaliplatin-based regimens.

Xeloda has also been used in combination with oxaliplatin for the treatment of advanced gastric cancer. Studies with Xeloda monotherapy indicate that Xeloda has activity in advanced gastric cancer.

Colon, colorectal and advanced gastric cancer: meta-analysis

A meta-analysis of six clinical trials (studies SO14695, SO14796, M66001, NO16966, NO16967, M17032) supports Xeloda replacing 5-FU in mono- and combination treatment in gastrointestinal cancer. The pooled analysis includes 3097 patients treated with Xeloda-containing regimens and 3074 patients treated with 5-FU-containing regimens. The hazard ratio for OS was 0.94 (95% CI: 0.89; 1.00, $p = 0.0489$) indicating that Xeloda-containing regimens are comparable to 5-FU – containing regimens.

Monotherapy- breast cancer

Data from two multicentre phase 2 clinical trials support the use of Xeloda monotherapy for 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. In these trials, a total of 236 patients were treated with Xeloda (1250 mg/m² 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.

Combination therapy - breast cancer

Data from one multicentre, randomised, controlled phase 3 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 randomised to treatment with Xeloda (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period) and docetaxel (75 mg/m² as a 1 hour intravenous infusion every 3 weeks). A total of 256 patients were randomised to treatment with docetaxel alone (100 mg/m² 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-randomised population (investigator assessment) were 41.6% (Xeloda + docetaxel) vs. 29.7% (docetaxel alone); $p = 0.0058$. Time to disease progression or death 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).

Data from two multicentre phase 2 clinical trials support the use of Xeloda monotherapy for 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. In these trials, a total of 236 patients were treated with Xeloda (1250 mg/m² twice daily for 2 weeks followed by a 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.

Pharmacokinetic Properties

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/m² on day 14 with administration after food intake, the peak plasma concentrations (C_{max} in mcg/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 mcg•h/mL were 7.75, 7.24, 24.6, 2.03 and 36.3.

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.

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 tumour tissues.

Formation of 5-FU occurs preferentially at the tumour site by the tumour-associated angiogenic factor dThdPase, thereby minimising the exposure of healthy body tissues to systemic 5-FU.

The plasma AUC of 5-FU is 6 to 22 times lower than that following an IV bolus of 5-FU (dose of 600 mg/m²). The metabolites of capecitabine become cytotoxic only after conversion to 5-FU and anabolites of 5-FU (see Pharmacological Properties and Effects).

5-FU is further catabolised to the inactive metabolites dihydro-5-fluoruracil (FUH₂), 5-fluoro-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) via dihydropyrimidine dehydrogenase (DPD), which is rate limiting.

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. The pharmacokinetics of capecitabine have been evaluated over a dose range of 502 - 3514 mg/m²/day. The parameters of capecitabine, 5'-DFCR and 5'-DFUR measured on days 1 and 14 were similar. The AUC of 5-FU was 30% - 35% 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.

After oral administration capecitabine metabolites are primarily recovered in the urine. Most (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 medicine.

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).

Pharmacokinetics in special populations

A population pharmacokinetic analysis was carried out after Xeloda treatment of 505 patients with colorectal cancer dosed at 1250 mg/m² 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.

Patients with hepatic impairment due to liver metastases

No clinically significant effect on the bioactivation and pharmacokinetics of capecitabine was observed in cancer patients with mildly to moderately impaired liver function due to liver metastases (see Special dosage instructions).

There are no pharmacokinetic data on patients with severe hepatic impairment.

Patients with 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 capecitabine 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 Special dosage instructions).

Elderly

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 Special dosage instructions and Pharmacokinetics in special populations subsection; Patients with renal impairment).

Race

In a 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 Xeloda in black patients were not different compared to white patients.

Pharmaceutical Particulars

Stability

This medicine should not be used after the expiry date shown on the pack.
Store below 30°C.

Medicine Classification

Prescription Medicine

Packs

Xeloda 150 mg tablets in packs of 60.
Xeloda 500 mg tablets in packs of 120.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

Name and Address

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