# Xeloda®
Capecitabine

## 1. DESCRIPTION
### 1.1. Therapeutic / Pharmacologic Class of Drug
Cytostatic agent

### 1.2. Type of Dosage Form
Tablets 150 mg and 500 mg.

### 1.3. Route of Administration
Oral

### 1.4. Qualitative and Quantitative Composition
Active ingredient: capecitabine

## 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.

*Colorectal cancer:*
Xeloda is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.
Xeloda is indicated for the treatment of metastatic colorectal carcinoma.

*Gastric Cancer*
Xeloda is indicated for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen.

### 2.2. Dosage and Administration
**Standard Dosage**
Xeloda should only be prescribed by a qualified physician experienced in the utilisation of anti-neoplastic agents. Xeloda tablets should be swallowed whole with water within 30 minutes after a meal. Xeloda tablets should not be crushed or cut. 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). 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 tables 1 and 2, respectively.

Monotherapy
*Colon, colorectal and breast cancer:*
The recommended monotherapy starting dose of Xeloda in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or of locally advanced or metastatic breast cancer is 1250 mg/m$^2$ administered twice daily (morning and evening; equivalent to 2500 mg/m$^2$ total daily dose) for 2 weeks followed by a 7-day rest period.
Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Combination therapy
*Breast cancer:*
In combination with docetaxel, the recommended starting dose of Xeloda is 1250 mg/m$^2$ twice daily for 2 weeks followed by a 7-day rest period, combined with docetaxel at 75 mg/m$^2$ as a 1-hour intravenous infusion every 3 weeks. Pre-medication 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.

*Colon, colorectal and gastric cancer:*
In combination treatment, the recommended starting dose of Xeloda should be reduced to 1000 mg/m$^2$ administered twice daily for 2 weeks followed by a 7-day rest period. (see section 3.1.2 Clinical/ Efficacy studies for further information).
The inclusion of bevacizumab in a combination regimen has no effect on the starting dose of Xeloda.
Premedication to maintain adequate hydration and anti-emesis according to the cisplatin and oxaliplatin product information should be started prior to cisplatin administration for patients receiving the Xeloda plus cisplatin or oxaliplatin combination.
Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Dose calculation
Xeloda dose is calculated according to body surface area. The following tables show examples of the standard and reduced dose calculations (see section "Dosage adjustments during treatment") for a starting dose of Xeloda of either 1250 mg/m$^2$ or 1000 mg/m$^2$.

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

| | Dose level 1250 mg/m$^2$ (twice daily) | | | | |
|---|---|---|---|---|---|
| | Full dose<br><br>1250 mg/m$^2$ | Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening) | | Reduced dose (75%)<br><br>950 mg/m$^2$ | Reduced dose (50%)<br><br>625 mg/m$^2$ |
| Body Surface Area (m$^2$) | Dose per administration (mg) | 150 mg | 500 mg | Dose per administration (mg) | Dose per administration (mg) |
| ≤1.26 | 1500 | - | 3 | 1150 | 800 |
| 1.27 - 1.38 | 1650 | 1 | 3 | 1300 | 800 |
| 1.39 - 1.52 | 1800 | 2 | 3 | 1450 | 950 |
| 1.53 - 1.66 | 2000 | - | 4 | 1500 | 1000 |
| 1.67 - 1.78 | 2150 | 1 | 4 | 1650 | 1000 |
| 1.79 - 1.92 | 2300 | 2 | 4 | 1800 | 1150 |
| 1.93 - 2.06 | 2500 | - | 5 | 1950 | 1300 |
| 2.07 - 2.18 | 2650 | 1 | 5 | 2000 | 1300 |
| ≥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<br><br>1000 mg/m$^2$ | Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening) | | Reduced dose (75%)<br><br>750 mg/m$^2$ | Reduced dose (50%)<br><br>500 mg/m$^2$ |
| Body Surface Area (m$^2$) | Dose per administration (mg) | 150 mg | 500 mg | Dose per administration (mg) | Dose per administration (mg) |
| ≤1.26 | 1150 | 1 | 2 | 800 | 600 |
| 1.27 - 1.38 | 1300 | 2 | 2 | 1000 | 600 |
| 1.39 - 1.52 | 1450 | 3 | 2 | 1100 | 750 |
| 1.53 - 1.66 | 1600 | 4 | 2 | 1200 | 800 |
| 1.67 - 1.78 | 1750 | 5 | 2 | 1300 | 800 |
| 1.79 - 1.92 | 1800 | 2 | 3 | 1400 | 900 |
| 1.93 - 2.06 | 2000 | - | 4 | 1500 | 1000 |
| 2.07 - 2.18 | 2150 | 1 | 4 | 1600 | 1050 |
| ≥2.19 | 2300 | 2 | 4 | 1750 | 1100 |

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.
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.

*Hematology:*
Patients with baseline neutrophil counts of <1.5 x 10$^9$ /l and/or thrombocyte counts of <100 x 10$^9$ /l should not be treated with Xeloda. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 hematologic toxicity, treatment with Xeloda should be interrupted.
If the neutrophil count drops below 1.0 x 10$^9$/L or if the platelet count drops below 75 x 10$^9$/L, capecitabine. At recovery, restart capecitabine at full dose.
The following table shows the recommended dose modifications following toxicity related to Xeloda:

**Table 3 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 | | 75 % |
| 3$^{rd}$ appearance | | 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 | | 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 (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. For hand-foot syndrome and hyperbilirubinemia, (see section 2.4, Warnings and Precautions).

General combination therapy
Dose modifications for toxicity when Xeloda is used in combination with other therapies should be made according to Table 3 above 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 drugs are met.
During a treatment cycle for those toxicities considered by the treating physician not to be related to Xeloda, Xeloda should be continued and the dose of the other agent adjusted according to the appropriate 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.

#### 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 adverse drug reactions (ADRs) were more frequent in patients over 80 years of age compared to younger patients.
When Xeloda was used in combination with other antineoplastic agents, geriatric patients (≥ 65 years) experienced more grade 3 and grade 4 ADRs and ADRs 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 ADRs and treatment-related serious ADRs 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/m$^2$ 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 800 mg/m$^2$ twice daily is recommended.

*Renal Impairment*
In patients with moderate renal impairment (creatinine clearance 30 - 50 ml/min [Cockroft and Gault]) at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m$^2$ 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 ADRs with subsequent dose adjustment as outlined in Table 3 above (see also section 3.2.5 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.

*Hepatic Impairment*
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 section 3.2.5, Pharmacokinetics in Special Populations and section 2.4, Warnings and Precautions). Patients with severe hepatic impairment have not been studied.

### 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.

As with other fluoropyrimidines, Xeloda is contraindicated in patients with known complete absence of dihydropyrimidine 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 2.4.2 Interactions with other Medicinal Products and other Forms of Interaction).

Xeloda is contraindicated in patients with severe leukopenia, neutropenia or thrombocytopenia.

Xeloda is contraindicated in patients with severe hepatic impairment.

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.

### 2.4. Warnings and Precautions
***Warnings***
*Diarrhea*: Xeloda can induce diarrhea, which can sometimes be severe. Patients with severe diarrhea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. Standard anti-diarrhea treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Dose reduction should be applied as necessary (see section 2.2, Dosage and Administration).

*Dehydration*: Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated. If Grade 2 (or higher) dehydration occurs, Xeloda treatment should be immediately interrupted and the dehydration corrected. 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).
Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic agents. Acute renal failure secondary to dehydration is potentially fatal, see section 2.6.2 Postmarketing Experience, Undesirable Effects.

*Dihydropyrimidine dehydrogenase (DPD) deficiency*: Based on postmarketing reports, patients with certain homozygous or certain compound heterozygous mutations in the *DPYD* gene locus that result in complete or near complete absence of DPD activity are at the highest risk for acute early-onset of toxicity and severe, life-threatening,

or fatal adverse reactions caused by XELODA (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with certain heterozygous *DPYD* variants (eg. *DPYD**2A variant) that may cause partial DPD deficiency have been shown to have increased risk of severe, life-threatening, or fatal adverse reactions caused by XELODA.
Testing for DPD deficiency should be considered based on the local availability and current guidelines.
Withhold or permanently discontinue XELODA based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity.
No XELODA dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specifictest.

***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.

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

*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).

*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.

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 (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. For patients receiving Xeloda monotherapy in the metastatic setting, the median time to onset was 79 days (range 11 to 360 days), with a severity range of Grades 1 to 3. Grade 1 hand-foot syndrome is defined by numbness, dysesthesia/paresthesia, tingling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 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 section 2.2, 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. There is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis in patients treated with Xeloda.

Xeloda can induce hyperbilirubinemia. 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.

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.

Care should be exercised when Xeloda is co-administered 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 Medical Products and other Forms of Interaction).

**2.4. General**
Dose limiting toxicities include 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 have to be withheld or reduced (see also section 2.2, Dosage and Administration).

**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.

*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. 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. In a study of single oral administration of Xeloda to lactating mice, a significant amount of capecitabine metabolites was detected in the 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 diarrhea, nausea and vomiting (see section 2.2.1, Special Dosage Instructions). When Xeloda was used in combination with other agents geriatric 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 ADRs and early withdrawals from treatment due to ADRs 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 section 3.2.5, Pharmacokinetics in Special Populations and section 2.2.1, Special Dosage Instructions).

**2.5.8. Effects on ability to drive and use machines**
Xeloda has minor or moderate influence on the ability to drive and use machines. Xeloda may cause dizziness, fatigue and nausea.

**2.6. Undesirable Effects**
**2.6.1. Clinical Trials**
*a. Summary of the safety profile*
The overall safety profile of Xeloda is based on data from over 3000 patients treated with Xeloda as monotherapy or Xeloda in combination with different chemotherapy regimens in multiple indications. The safety profiles of Xeloda monotherapy for the metastatic breast cancer, metastatic colorectal cancer and adjuvant colon cancer populations are comparable. See section 3.1 for details of major studies, including study designs and major efficacy results.
The most commonly reported and/or clinically relevant treatment-related adverse drug reactions (ADRs) were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), hand-foot syndrome (palmar-plantar erythrodysesthesia), fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism.

*b. Tabulated summary of adverse reactions*
ADRs considered by the investigator to be possibly, probably, or remotely related to the administration of Xeloda are listed in Table 4 for Xeloda given as a single agent and in Table 5 for Xeloda given in combination with different chemotherapy regimens in multiple indications. The following headings are used to rank the ADRs by frequency: very common (≥ 1/10), common (≥ 1/100, < 1/10) and uncommon (≥ 1/1,000, < 1/100). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Xeloda Monotherapy:
Table 4 lists ADRs associated with the use of Xeloda monotherapy based on a pooled analysis of safety data from three major studies including over 1900 patients (studies M66001, SO14695, and SO14796). ADRs are added to the appropriate frequency grouping according to the overall incidence from the pooledanalysis.

**Table 4 Summary of related ADRs reported in patients treated with Xeloda monotherapy**

| **Body System** | **Very Common** ***All grades*** | ***Common*** ***All grades*** | **Uncommon** ***Severe and/or Lifethreatening (grade 3-4) or considered medically relevant*** |
|---|---|---|---|
| *Infections and infestations* | - | Herpes viral infection, Nasopharyngitis, Lower respiratory tract infection | Sepsis, Urinary tract infection, Cellulitis, Tonsillitis, Pharyngitis, Oral candidiasis, Influenza, Gastroenteritis, Fungal infection, Infection, Tooth abscess |
| *Neoplasm benign, malignant and unspecified* | - | - | Lipoma |
| *Blood and lymphatic system disorders* | - | Neutropenia, Anaemia | Febrile neutropenia, Pancytopenia, Granulocytopenia, Thrombocytopenia, Leucopenia, Haemolytic anaemia, International Normalised Ratio (INR) increased/Prothrombin time prolonged |
| *Immune system disorders* | - | - | Hypersensitivity |
| *Metabolism and nutrition disorders* | Anorexia | Dehydration, Decreased appetite, Weight decreased | Diabetes, Hypokalaemia, Appetite disorder, Malnutrition, Hypertriglyceridaemia |
| *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 disorders* | - | - | Vertigo, Ear pain |
| *Cardiac disorders* | - | - | Angina unstable, Angina pectoris, Myocardial ischaemia, 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 | Intestinal obstruction, Ascites, Enteritis, Gastritis, Dysphagia, Abdominal pain lower, Oesophagitis, Abdominal discomfort, Gastrooesophageal reflux disease, Colitis, Blood in stool |
| *Hepatobiliary Disorders* | - | Hyperbilirubinemia , Liver function test abnormalities | Jaundice |
| *Skin and subcutaneous tissue disorders* | *Palmar-plantar erythrodyesthesia syndrome, Dermatitis | Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyperpigmentation, Rash macular, Skin desquamation, Pigmentation disorder, Nail disorder | Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome |
| *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, Blood creatinine increased |
| *Reproductive system and breast disorders* | - | - | Vaginal haemorrhage |
| *General disorders and administration site conditions* | Fatigue, Asthenia | Pyrexia, Lethargy, Oedema peripheral, Malaise, Chest pain | Oedema, Chills, Influenza like illness, Rigors, Body temperature increased |
| *Injury, poisoning and procedural complications* | - | - | Blister, Overdose |

* Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints (see section 2.4 Warnings and Precautions).

Xeloda in combination therapy:
Table 5 lists ADRs associated with the use of Xeloda in combination with different chemotherapy regimens in multiple indications based on safety data from over 1400 patients. ADRs are added to the appropriate frequency grouping (Very common or Common) according to the highest incidence seen in any of the major clinical trials and are only added when they were seen **in addition** to those seen with Xeloda monotherapy or seen at **a higher frequency grouping** compared to Xeloda monotherapy (see Table 4). Uncommon ADRs reported for Xeloda in combination therapy are consistent with the ADRs reported for Xeloda monotherapy or reported for monotherapy with the combination agent (in literature and/or respective summary of product characteristics).
Some of the ADRs are reactions commonly seen with the combination agent (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin), or with bevacizumab (e.g. hypertension); however an exacerbation by Xeloda therapy cannot be excluded.

**Table 5 Summary of related ADRs reported in patients treated with Xeloda in combination treatment in addition to those seen with Xeloda monotherapy or seen at a higher frequency grouping compared to Xeloda monotherapy**

| Body System | Very Common *All grades* | Common *All grades* |
|---|---|---|
| *Infections and infestations* | - | Herpes zoster, Urinary tract infection, Oral candidiasis, Upper respiratory tract infection , Rhinitis, Influenza, +Infection, oral herpes |
| *Blood and lymphatic system disorders* | +Neutropenia, +Leukopenia, +Anemia, +Neutropenic fever, Thromboyctopenia | Bone marrow depression, +Febrile Neutropenia |
| *Immune system disorders* | - | Hypersensitivity |
| *Metabolism and nutrition disorders* | Appetite decreased | Hypokalaemia, Hyponatremia, Hypomagnesaemia, Hypocalcaemia, Hyperglycaemia |
| *Psychiatric disorders* | - | Sleep disorder, Anxiety |
| *Nervous system disorders* | Paraesthesia and dysaesthesia, Peripheral neuropathy, Peripheral sensory neuropathy, Dysgeusia, Headache | Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia |
| *Eye disorders* | Lacrimation increased | Visual disorders, Dry eye, Eye pain, Visual impairment, Vision blurred |
| *Ear and labyrinth disorders* | - | Tinnitus, Hypoacusis |
| *Cardiac disorders* | - | Atrial fibrillation, Cardiac ischemia/infarction |
| *Vascular Disorders* | Lower limb oedema, Hypertension, +Thrombosis/embolism | Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis |
| *Respiratory, thoracic and mediastinal system disorders* | Sore throat, Dysaesthesia pharynx | Hiccups, Pharyngolaryngeal pain, Dysphonia |
| *Gastrointestinal disorders* | Constipation, Dyspepsia | Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastroesophageal reflux disease, Oral pain, Dysphagia, Rectal haemorrhage, Abdominal pain lower, Oral dysaesthesia, Paraesthesia oral, Hypoaesthesia oral, Abdominal discomfort |
| *Hepatobiliary disorders* | - | Hepatic function abnormal |
| *Skin and subcutaneous tissue disorders* | Alopecia, Nail disorder | Hyperhidrosis, Rash erythematous, Urticaria, Night sweats |
| *Musculoskeletal and connective tissue disorders* | Arthragia, Myalgia, Pain in extremity | Pain in jaw , Muscle spasms, Trismus, Muscular weakness |
| *Renal and urinary disorder* | - | Haematuria, Proteinuria, Creatinine renal clearance decreased, Dysuria |
| *General disorders and administration site conditions* | Pyrexia, Weakness, +Lethargy, Temperature intolerance | Mucosal inflammation, Pain in limb, Pain, Chills, Chest pain, Influenza-like illness, +Fever, Infusion related reaction, Injection site reaction, Infusion site pain, Injection site pain |
| *Injury, poisoning and procedural complications* | - | Contusion |

+ For each term, the frequency count was based on ADRs of all grades. For terms marked with a "+", the frequency count was based on grade 3-4 ADRs. ADRs are added according to the highest incidence seen in any of the major combination trials.

**2.6.2. Postmarketing Experience**

The following additional serious adverse reactions have been identified during post-marketing 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); and uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (≥ 1/1,000 to < 1/100); unknown (cannot be estimated from the available data).

**Table 6 Adverse Drug Reactions from Postmarketing Experience**

| Sytem Organ Class | 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 |
| **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, diarrhea, nausea, gastric irritation, and vomiting.

**2.7. Overdose**

The manifestations of acute overdose include nausea, vomiting, diarrhea, 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. These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. 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. Patients taking coumarin-derivative anticoagulants concomitantly with Xeloda should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anti-coagulant dose adjusted accordingly (See Section 2.4 Warning 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 co-administered 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 3.2.1).

*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: 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.

*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.

*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.

*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.

## 3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

### 3.1. Pharmacodynamic Properties

#### 3.1.1. Mechanism of Action

Capecitabine is a fluoropyrimidine carbamate derivative that was designed as an orally administered, tumor-activated and tumor-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 tumor site by the tumor-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 tumor tissues. Following oral administration of capecitabine to patients with colorectal cancer (N=8), the ratio of 5-FU concentration in colorectal tumors vs adjacent tissues was 3.2 (range 0.9 to 8.0). The ratio of 5-FU concentration in tumor vs 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 4 times greater in primary colorectal tumor than in adjacent normal tissue.

Several human tumors, 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 cells and tumor 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 N$^{5\text{-}10}$-methylenetetrahydrofolate 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.

#### *3.1.2.* Clinical / Efficacy Studies

***Colon and Colorectal Cancer***

*Monotherapy in adjuvant colon cancer*

Data from one multicenter, randomized, controlled phase 3 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: M66001). 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 i.v. followed by 425 mg/m$^2$ i.v. bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks). Xeloda was at least equivalent to i.v. 5-FU/LV in disease-free survival (p=0.0001, non-inferiority margin 1.2). In the all-randomized population, tests for difference of Xeloda vs 5-FU/LV in disease-free survival and overall survival showed hazard ratios of 0.88 (95% CI 0.77 – 1.01; p = 0. 068) and 0.86 (0.74 – 1.01; p= 0.060), respectively. The median follow up at the time of the analysis was 6.9 years.

*Combination therapy in adjuvant colon cancer*

Data from one multicentre, randomised, controlled phase 3 clinical trial in patients with stage III (Dukes' C) colon cancer supports the use of Xeloda in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer (NO16968 study). In this trial, 944 patients were randomised to 3-week cycles for 24 weeks with Xeloda (1000 mg/m$^2$ twice daily for 2 weeks followed by a 1-week rest period) in combination with oxaliplatin (130 mg/m$^2$ intravenous infusion over 2-hours on day 1 every 3 weeks); 942 patients were randomized to bolus 5-FU and leucovorin. In the primary analysis for DFS, in the ITT population, 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) which translates into a 13% reduction in risk of death. The 5 year OS rate was 78% for XELOX versus 74% for 5-FU/LV. The efficacy data provided is based on a median observation time of 59 months for OS and 57 months for DFS. The rate of withdrawal due to adverse events was higher in the XELOX combination therapy arm (21%) as compared with that of the 5-FU/LV monotherapy arm (9%) in the ITT population.
At 7 years median follow up, XELOX maintained a statistically significant superior disease-free survival HR=0.80 (95% CI 0.69, 0.93; p=0.0038), and relapse-free survival HR=0.78 (95% CI 0.67, 0.91; p=0.0015). The OS rate at 7 years was 73% in the XELOX arm and 67% in the 5-FU/LV arm. The additional two years of follow up after the primary analysis show an increase in the difference between survival rates from 3% to 6%.

*Monotherapy in metastatic colorectal cancer*

Data from two identically designed, multicenter, 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/m$^2$ 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/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-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 multicenter, randomized, controlled phase 3 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 metastastic colorectal cancer. The study contained two parts: an initial 2-arm part in which patients were randomized to two different treatment groups, including XELOX or FOLFOX-4, and a subsequent 2x2 factorial part with four different treatment groups, including XELOX + placebo (P), FOLFOX-4+P, XELOX+BV, and FOLFOX-4+BV. The treatment regimens are summarized in the table below.

**Table 7 Treatment regimens in Study NO16966**

| | Treatment | Starting Dose | Schedule |
|---|---|---|---|

| | | | |
|---|---|---|---|
| FOLFOX-4 Or FOLFOX-4 + Avastin | Oxaliplatin | 85 mg/m² i.v. 2 h | Oxaliplatin on Day 1, every 2 weeks. |
| | Leucovorin | 200 mg/m² i.v. 2 h | Leucovorin on Day 1 and 2, every 2 weeks. |
| | 5-Fluorouracil | 400 mg/m² i.v. bolus, 600 mg/ m² i.v. 22 h | 5-fluorouracil i.v. bolus/infusion, each on Day 1 and 2, every 2 weeks. |
| | Placebo or Avastin | 5 mg/kg i.v. 30-90m | |
| XELOX or XELOX +Avastin | Oxaliplatin | 130 mg/m² i.v. 2 h | Oxaliplatin on Day 1, every 3 weeks |
| | Capecitabine | 1000 mg/m² oral bid | Capecitabine oral bid for 2 weeks (followed by 1-week off treatment) |
| | Placebo or Avastin | 7.5 mg/kg i.v. 30 -90m | Day 1, prior to XELOX, every 3 weeks |
| 5-Fluorouracil: i.v. 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 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 8 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

*Combination therapy – Second-line treatment of colorectal cancer*
Data from a multicenter, randomized, controlled phase III clinical study (NO16967) support the use of Xeloda in combination with oxaliplatin for the second-line treatment of metastastic colorectal cancer. In this trial, 627 patients with metastatic colorectal carcinoma who have received prior treatment with irinotecan in combination with a fluoropyrimidine regimen as first-line therapy were randomized to treatment with XELOX or FOLFOX-4. For the dosing schedule of XELOX and FOLFOX-4 (without addition of placebo or bevacizumab), refer to Table 7. 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 9). 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 Table 9.

**Table 9 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 multicenter, randomized, controlled phase 3 clinical trial in patients with advanced gastric cancer supports the use of Xeloda for the first-line treatment of advanced gastric cancer (ML17032). In this trial, 160 patients were randomized 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 randomized 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 (see table below).

**Table 10 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 gastric cancer supports the use of Xeloda for the first-line treatment of advanced gastric cancer (REAL-2). 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 infusionvia 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 givenas 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 - 0.99) and for oxaliplatin- vs cisplatin-based regimens (hazard ratio 0.92; 95% CI 0.80 - 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 overall survival was 0.94 (95% CI: 0.89; 1.00, p=0.0489) with Xeloda-containing regimens indicating that they are non-inferior to 5-FU-containing regimens.

*Combination therapy- breast cancer*
Data from one multicenter, 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).

*Monotherapy- Breast carcinoma*
Data from two multicenter 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.

## 3.2. Pharmacokinetic Properties

### 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/m² 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.

Formation of 5-FU occurs preferentially at the tumor site by the tumor-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 i.v. 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 section 3.1.1, Mechanism of Action).

5-FU is further catabolized to the inactive metabolites dihydro-5-fluorouracil ($FUH_2$), 5-fluoro-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) via dihydropyrimidine dehydrogenase (DPD), which is rate limiting.

### 3.2.4. Elimination
The elimination half-lifes ($t_{1/2}$ 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. Fecal 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 ofcapecitabine).

### 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/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.

*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 section 2.2.1, Special Dosage Instructions).
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 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 section 2.2.1, Special Dosage Instructions and section 3.2.5, Pharmacokinetics in Special Populations, subsection RenalImpairment).

*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 from those in white patients.

## 3.3. Nonclinical Safety

### 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 (ie, 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
Oral administration of capecitabine to pregnant mice during the period of organogenesis at a dose of 198 mg/kg/day caused malformations and embryo lethality. 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.

## 4. PHARMACEUTICAL PARTICULARS

### 4.1. Storage

This medicine should not be used after the expiry date (EXP) shown on the pack. Store in the original package in order to protect from moisture.

### 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.

### 4.3. Packs

| | |
|---|---|
| Film-coated tablets 150 mg | 60 |
| Film-coated tablets 500 mg | 120 |

Medicine: keep out of reach of children

Current at Oct 2022

CHEPLAPHARM Arzneimittel GmbH, Greifswald, Germany