Xeloda®

Capecitabine

COMPOSITION

Active ingredient: capecitabine

Excipients: lactose anhydrous, croscarmellose sodium (produced from genetically modified cotton), hypermellose, cellulose microcrystalline, magnesium stearate, talc, titanium dioxide, yellow iron oxide, red iron oxide

PHARMACEUTICAL FORM AND QUANTITY OF ACTIVE SUBSTANCE PER UNIT

Peach film-coated tablets containing 150 mg of capecitabine

Light-peach film-coated tablets containing 500 mg of capecitabine

INDICATIONS AND POTENTIAL USES

Colon and colorectal cancer

Adjuvant treatment of patients with Dukes' C colon cancer either as monotherapy or in combination with oxaliplatin.

First-line therapy in patients with metastatic colorectal cancer either as monotherapy or in combination with oxaliplatin (XELOX) with or without bevacizumab.

Second-line therapy in patients with metastatic colorectal cancer in combination with oxaliplatin (XELOX).

Breast cancer

In combination with docetaxel in patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy with anthracyclines.

In combination with vinorelbine in patients with locally advanced or metastatic breast cancer after failure of treatment with anthracyclines and taxanes.

In patients with locally advanced or metastatic breast cancer after failure of paclitaxel and chemotherapy with anthracyclines.

Esophageal cancer, cancer of the gastroesophageal junction and gastric cancer

First-line therapy in combination with epirubicin and oxaliplatin in patients with advanced or metastatic gastric cancer, esophageal cancer or cancer of the gastroesophageal junction.

In combination with Herceptin and cisplatin in patients with HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction who have not received chemotherapy for their metastatic disease. Herceptin should only be used in patients with

metastatic gastric cancer whose tumors overexpress HER2, as defined by IHC2+ and confirmed by FISH+ or IHC3+, determined by a validated assay.

DOSAGE AND ADMINISTRATION

Standard dosage

Xeloda film-coated tablets are to be taken with water within 30 minutes after a meal.

Adjuvant therapy in Dukes' C colon cancer

Monotherapy (6 months)

The recommended dose of Xeloda in monotherapy is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to a total daily dose of 2500 mg/m^2) for 14 days followed by a 7-day rest period.

In combination with oxaliplatin (6 months)

Following administration of oxaliplatin as a 130 mg/m^2 intravenous infusion over 2 hours, treatment with Xeloda 1000 mg/m^2 twice daily is started on the same day and given over 2 weeks followed by a 7-day rest period. Detailed information on the use of oxaliplatin and on administration of premedication is given in the prescribing information for oxaliplatin.

Treatment of metastatic colorectal cancer

Monotherapy

The recommended dose of Xeloda in monotherapy is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to a total daily dose of 2500 mg/m^2) for 14 days followed by a 7-day rest period.

In combination with oxaliplatin

Following administration of oxaliplatin as a 130 mg/m^2 intravenous infusion over 2 hours, treatment with Xeloda 1000 mg/m^2 twice daily is started on the same day and given over 2 weeks followed by a 7-day rest period. Detailed information on the use of oxaliplatin and on administration of premedication is given in the prescribing information for oxaliplatin.

In combination with oxaliplatin and bevacizumab

Bevacizumab is administered as a 7.5 mg/kg intravenous infusion over 30 to 90 minutes on day 1 of the 3-weekly cycle followed by oxaliplatin and Xeloda as described in *In combination with oxaliplatin*. For detailed information, please refer to the prescribing information for Avastin.

Treatment of locally advanced or metastatic breast cancer

Monotherapy

The recommended dose of Xeloda in monotherapy is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to a total daily dose of 2500 mg/m^2) for 14 days followed by a 7-day rest period.

In combination with docetaxel

In combination therapy with docetaxel the recommended dose of Xeloda is 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel 75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks. This 3-weekly cycle should be continued until progression of the cancer is documented or intolerable side effects necessitate cessation of treatment. Detailed information on the use of docetaxel and on administration of premedication is given in the prescribing information for docetaxel.

In combination with vinorelbine

The recommended dose of Xeloda is 1000 mg/m^2 twice daily for 14 days, followed by a 7-day rest period. Detailed information on the use of vinorelbine is given in the prescribing information for vinorelbine.

Treatment of advanced or metastatic gastric cancer, esophageal cancer or cancer of the gastroesophageal junction

In combination with oxaliplatin and epirubicin

The recommended dose of Xeloda is 625 mg/m^2 twice daily with no treatment break for 24 weeks in combination with oxaliplatin 130 mg/m^2 (every 3 weeks) and epirubicin 50 mg/m^2 (every 3 weeks). For detailed information on premedication to maintain adequate hydration and antiemesis before oxaliplatin administration, see the prescribing information on oxaliplatin.

Treatment of HER2-positive metastatic adenocarcinoma of the stomach or gastroesophageal junction

In combination with Herceptin and cisplatin

Following Herceptin and cisplatin (80 mg/m^2) given as a 2-hour intravenous infusion, treatment is started on the same day with Xeloda 1000 mg/m^2 twice daily for two weeks, followed by a 7-day rest period, continued for 6 cycles. Detailed information on the use of Herceptin and cisplatin and on administration of a premedication can be found in the relevant prescribing information.

The following tables show how the standard dose and the reduced dose of Xeloda (see *Dosage adjustment during treatment*) are calculated for a 1250 mg/m^2 or 1000 mg/m^2 starting dose of Xeloda.

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

	Dose level 1250 mg/m² (twice daily)				
	Full dose 1250 mg/m²	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/m²	Reduced dose (50%) 625 mg/m²
Body surface area (m²)	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
³ 2.19	2800	2	5	2150	1450

Table 2: Standard and reduced dose calculations according to body surface area for a Xeloda starting dose of 1000 mg/m²

	Dose level 1000 mg/m² (twice daily)				
	Full dose 1000 mg/m²	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/m²	Reduced dose (50%) 500 mg/m²
Body surface area (m²)	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
³ 2.19	2300	2	4	1750	1100

Dosage adjustment during treatment
Possible side effects of Xeloda can be managed by symptomatic treatment and/or modification of the Xeloda dose (treatment interruption and/or dose reduction). Once the dose has been reduced it should not be increased at a later time.

Patients taking Xeloda should be informed of the need to interrupt treatment immediately if moderate or severe side effects occur. Doses of Xeloda omitted because of side effects are not replaced; instead, the patient should resume the originally planned treatment cycle. Depending on the severity of the side effects, the following dose modifications are recommended:

Table 3: Summary of dose adjustments of Xeloda

Toxicity NCIC grades	Measures to be taken if side effects occur	Dose adjustment for next cycle (% of starting dose)
Grade 2		
First appearance	Interrupt until resolved to grade 0–1	100%
Second appearance	Interrupt until resolved to grade 0–1	75%
Third appearance	Interrupt until resolved to grade 0–1	50%
Fourth appearance	Discontinue treatment permanently	–
Grade 3		
First appearance	Interrupt until resolved to grade 0–1	75%
Second appearance	Interrupt until resolved to grade 0–1	50%
Third appearance	Discontinue treatment permanently	–
Grade 4		
First appearance	Discontinue treatment permanently or if physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0–1	– / 50%
Second appearance	Discontinue treatment permanently	–

Hematology: Patients with baseline neutrophil counts of < 1.5×10^9/l and/or platelet counts of <100×10^9/l should not be treated with Xeloda. If laboratory assessments during a treatment cycle show grade 3 or 4 hematological toxicity, treatment with Xeloda should be interrupted until the toxicity has resolved to grade 0–1.

Special dosage instructions

Hepatic impairment: The pharmacokinetics of Xeloda were studied in patients with mild to moderate metastasis-induced elevations in bilirubin, transaminases and alkaline phosphatase. No dosage adjustment is required in these patients. Administration of Xeloda should be interrupted if treatment-related elevations in bilirubin of >3.0×ULN (upper limit of normal) or treatment-related elevations in hepatic aminotransferases (ALAT, ASAT) of >2.5×ULN occur. Treatment with Xeloda may be resumed when bilirubin decreases to <3.0×ULN or hepatic aminotransferases decrease to <2.5×ULN.

No experience is available in patients with hepatic impairment. In patients with mild to moderate hepatic impairment the use of capecitabine should be carefully monitored; in patients with severe hepatic impairment (Child-Pugh C) Xeloda is contraindicated (see *Contraindications*).

Renal impairment: In patients with mild renal impairment (creatinine clearance 51–80 ml/min) no adjustment in starting dose is required. In patients with moderate renal impairment (creatinine clearance 30–50 ml/min) at baseline the dose of Xeloda should be reduced to 75% of the recommended starting dose (see *Warnings and precautions*). In patients with severe renal impairment (creatinine clearance < 30 ml/min) Xeloda is contraindicated (see *Contraindications*). If the calculated creatinine clearance falls to < 30 ml/min during treatment, Xeloda should be stopped.

Children and adolescents (under 18 years): No studies have been performed on the tolerability and efficacy of Xeloda in children and adolescents.

Elderly patients: Grade 3/4 treatment-related side effects were more frequent in the elderly (over 60 years) than in younger patients.

No adjustment of the starting dose is required for Xeloda monotherapy or combination with oxaliplatin, but careful monitoring is advised.

In combination with docetaxel it is recommended that the Xeloda starting dose be reduced to 75%.

CONTRAINDICATIONS

Hypersensitivity to the active ingredient, to other fluoropyrimidines (fluorouracil [5-FU]) or to one of the excipients.

Known severe dihydropyrimidine dehydrogenase (DPD) deficiency (see *Warnings and precautions).*

Pregnancy and lactation.

Severe renal impairment (creatinine clearance under 30 ml/min).

Severe hepatic impairment (Child-Pugh C).

Concomitant treatment with brivudine or with chemically related substances, such as sorivudine (see *Interactions*).

WARNINGS AND PRECAUTIONS

Xeloda should be prescribed only by a suitably qualified doctor with experience in the use of antineoplastic drugs. Since Xeloda is usually taken at home, patients must be informed of the possible side effects before starting treatment and specifically told what to do should such effects occur. Patients receiving Xeloda should be closely monitored for side effects.

Most side effects are reversible and do not require permanent discontinuation of therapy, though in certain situations it may be necessary to interrupt treatment and/or reduce the dosage (see *Dosage and administration*, *Dose adjustment during treatment*).

Dose-limiting side effects include diarrhea, hand-foot syndrome, nausea, stomatitis and abdominal pain.

Diarrhea: Diarrhea of all degrees of severity has been observed in 50% of patients. Patients with severe diarrhea should be carefully monitored and, if they become dehydrated, should be given fluid and electrolyte replacement. Standard antidiarrheal treatment (e.g. loperamide) should be initiated in accordance with medical indications as soon as possible. If necessary the dose should be reduced.

Dehydration: Dehydration should be prevented or corrected at the onset. Nausea, vomiting or diarrhea can rapidly lead to dehydration. Fatal renal failure has been reported in patients with pre-existing renal impairment or comedicated with known nephrotoxic agents. 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*).

Dihydropyrimidine dehydrogenase (DPD) deficiency: Rare cases of unexpected severe toxicity associated with 5-FU (e.g. stomatitis, diarrhea, mucosal inflammation, neutropenia and neurotoxicity) have been attributed to a deficiency of DPD activity. Patients with low or absent DPD activity, an enzyme involved in fluorouracil degradation, are at increased risk of severe, life-threatening or fatal adverse reactions caused by fluorouracil, and are contraindicated from using Xeloda (see *Contraindications*). Such patients with certain homozygous or certain compound heterozygous mutations in the DPYD gene locus that cause complete or near-complete absence of DPD activity, have the highest risk of life-threatening or fatal toxicity and should not be treated with Xeloda. No dose has been proven safe for patients with complete absence of DPD activity.

Patients with partial DPD deficiency in whom the benefits of Xeloda are considered to outweigh the risks (taking into account the possible suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen) must be treated with extreme caution, initially with a substantial dose reduction and frequent subsequent monitoring and dose adjustment according to toxicity.

In patients with unrecognized DPD deficiency treated with capecitabine, life-threatening toxicities manifesting as overdose may occur. In the event of grade 2–4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities (see *Overdosage*).

Hand-foot syndrome: Xeloda can cause hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) with a severity of between 1 and 3. In patients on Xeloda monotherapy the median interval until first occurrence is 79 days (11 – 360 days). Hand-foot syndrome grade 1 is characterized by numbness, dysesthesia/paresthesia, tingling, erythema or painless swelling of the hands and/or feet. The symptoms do not interfere with normal daily activities. Grade 2 is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's normal daily activities. Grade 3 hand-foot syndrome is defined as moist desquamation,

ulceration, blistering and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform normal daily activities. If grade 2 or 3 hand-foot syndrome occurs, the Xeloda dose should be adjusted (see *Dosage and administration, Dose adjustment during treatment*).

Xeloda can induce severe skin reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see *Undesirable effects*). Xeloda should be permanently discontinued in patients who experience a severe skin reaction during treatment.

In the absence of tolerability and efficacy data in patients with hepatic impairment, capecitabine use should be carefully monitored in patients with mild to moderate liver dysfunction, regardless of the presence or absence of liver metastases. In patients with liver metastases and elevations in bilirubin or other liver enzymes, Xeloda should be used with caution (see *Dosage and administration*, *Special dosage instructions*).

Xeloda should be used with caution in patients with renal impairment. In patients with moderate renal impairment (creatinine clearance 30 – 50 ml/min) a higher incidence of grade 3 or 4 side effects was observed, as was also the case with 5-FU. In these patients Xeloda should be reduced to 75% of the recommended starting dose.

The cardiotoxic side effects observed during treatment with Xeloda, such as myocardial infarction, angina pectoris, cardiac arrhythmias, cardiac arrest, heart failure and ECG changes, are comparable to those of other fluorinated pyrimidines. The incidence of such side effects is greater in patients with a history of coronary heart disease. Caution must be exercised in patients with a history of severe cardiac disease, arrhythmias and angina pectoris.

In elderly patients aged between 60 and 79 years treated for metastatic colorectal tumours with Xeloda monotherapy, the incidence of gastrointestinal side effects was similar to that in the overall patient population. Among very elderly patients (80 years and older), there was a higher per cent incidence of reversible grade 3 or 4 gastrointestinal side effects such as diarrhea, nausea and vomiting (see *Dosage and administration*, *Special dosage instructions*).

Evaluation of the safety data of patients aged ³ 60 years treated with the combination of Xeloda and docetaxel showed an increased incidence of treatment-related side effects compared with patients under 60 years. Early discontinuation of treatment may be necessary.

Xeloda film-coated tablets contain lactose and should not be administered to patients with the rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

INTERACTIONS

Protein binding: Capecitabine plasma protein binding is low (54%). Interaction due to displacement of highly protein-bound substances is therefore not to be expected.

Coumarin-type anticoagulants: Changes in coagulation parameters and/or bleeding have been reported in patients who took capecitabine together with coumarin derivatives such as warfarin and phenprocoumon (CYP2C9 substrates). These undesirable effects appeared within a few days or up to several months after initiation of treatment with capecitabine, and in isolated cases within a month of suspension of treatment with capecitabine. In a clinical interactions 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. Patients taking coumarin-type anticoagulants (incl. acenocoumarol) concomitantly with capecitabine must be regularly monitored for changes in coagulation parameters (thromboplastin time or INR) and the anticoagulant dose adjusted accordingly.

Phenytoin: Increased plasma concentrations of phenytoin (a CYP2C9 substrate) have been observed during concomitant use of Xeloda with phenytoin. Patients taking phenytoin concomitantly with Xeloda should be regularly monitored for increased plasma phenytoin concentrations and associated clinical symptoms.

Other CYP2C9 substrates: No interaction studies with other CYP2C9 substrates have been carried out. Caution is advisable if administering such drugs concomitantly with Xeloda.

Antacids: Ingestion of Xeloda together with an antacid containing aluminium hydroxide and magnesium hydroxide (Maalox) resulted in a slight increase in plasma concentrations of capecitabine and one metabolite (5'-DFCR); no effects were observed on the three major metabolites (5'-DFUR, 5-FU and FBAL).

Allopurinol: Interactions between allopurinol and 5-FU have been reported. Concomitant use of allopurinol and capecitabine should be avoided.

Docetaxel/paclitaxel: Studies examining the effects of Xeloda on the pharmacokinetics of docetaxel and paclitaxel and vice versa showed the pharmacokinetics of docetaxel or paclitaxel (C_{max} and AUC) to be unaffected by Xeloda and the pharmacokinetics of 5'-DFUR to be unaffected by docetaxel or paclitaxel.

Leucovorin (folinic acid): Leucovorin has no effect on the pharmacokinetics of capecitabine and its metabolites. However, leucovorin has an effect on the pharmacodynamics of capecitabine and the toxicity of capecitabine may be increased by leucovorin: the maximum tolerated dose of capecitabine alone using the intermittent regimen is 3000 mg/m^2 per day, whereas it is only 2000 mg/m^2 per day when capecitabine is combined with leucovorin (30 mg orally twice daily).

Brivudine and analogues: Capecitabine must not be used in combination with brivudine, an irreversible inhibitor of dihydropyrimidine dehydrogenase (DPD), or with chemically related substances such as sorivudine, as inhibition of this enzyme can intensify the toxicity of capecitabine with potentially fatal consequences. In addition, an interval of at least 4 weeks must be observed between treatment with brivudine or chemically related substances such as sorivudine and the start of capecitabine therapy.

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

PREGNANCY AND LACTATION

No studies have been conducted on the use of Xeloda in pregnant women. In reproductive toxicology studies in animals, capecitabine administration caused embryolethality and teratogenicity. These results are to be expected with fluoropyrimidine derivatives. It must be assumed that the use of Xeloda during pregnancy may damage the fetus. The substance should be regarded as teratogenic in humans. Xeloda should not be used during pregnancy. If Xeloda is administered during pregnancy or the patient becomes pregnant during treatment, the patient must be informed about the potential risk to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Xeloda. Women and men receiving treatment with Xeloda should employ contraceptive measures.

It is not known whether Xeloda is excreted in breast milk. In a study in which suckling mice were given a single oral dose of Xeloda, significant amounts of capecitabine metabolites were detected in milk. Breastfeeding should therefore be avoided during treatment with Xeloda.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Xeloda may cause dizziness, fatigue and nausea. These effects may impair the ability to drive and use machines.

UNDESIRABLE EFFECTS

In clinical studies, the most commonly reported treatment-related side effects were diarrhea, nausea, vomiting, stomatitis and hand-foot syndrome (palmar-plantar erythrodysesthesia).

The undesirable effects of the combination of Xeloda with oxaliplatin and/or bevacizumab correspond to the undesirable effects that have been reported with Xeloda or oxaliplatin monotherapy or bevacizumab combination therapy (see prescribing information for oxaliplatin and bevacizumab).

Frequency rankings: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), very rare (<1/10,000, including individual case reports).

Infections

Very common: rhinopharyngitis (up to 13% in combination with Herceptin + cisplatin).

Common: Herpes simplex infections, oral candidiasis, pneumonia, septic shock (both in combination with Herceptin + cisplatin), cystitis (in combination with cisplatin).

Rare: local and fatal systemic infections (of bacterial, viral or fungal etiology).

Immune system

Common: hypersensitivity reactions, mainly in combination with oxaliplatin or Herceptin + cisplatin.

Blood and lymphatic system

Very common: lymphocytopenia (51.3–58.2%, grade 3/4 2.1–5.1%), anemia (2–41.4%, grade 3/4 1%, in combination with cisplatin or oxaliplatin with or without epirubicin 17–79%, grade 3/4 3–10.5%), thrombocytopenia (5–21.1%, grade 3/4 0.5–5.2%), neutropenia (1–30.3%, grade 3/4 <1–6%, in combination with docetaxel: 80.8%, grade 3/4: 62.9%, in combination with cisplatin with or without epirubicin: 33–85.6%, grade 3/4 16–51.1%), febrile neutropenia (mainly in combination with docetaxel and cisplatin with or without epirubicin: <1–16 %, grade 3/4 6.7%), leukopenia (3–14%, grade 3/4 3%).

Common: granulocytopenia.

Uncommon: pancytopenia, bone marrow depression.

Metabolism and nutrition disorders

Very common: anorexia (9–50%, grade 3/4 3%), hyperglycemia (40%, grade 3/4 0.9%), hypocalcemia (13.2%, grade 3/4 0.8%), hyponatremia (3–17.5%, grade 3/4 0.4–1%), reduced appetite (5–10%).

Common: hypercalcemia, hypokalemia, dehydration, weight loss.

Psychiatric disturbances

Common: depression, anxiety.

Nervous system

Very common, mainly in combination with oxaliplatin, docetaxel or cisplatin with or without epirubicin: taste disturbance (0–15%, grade 3/4 <1%), paresthesia (2–37%, grade 3/4 0–6%), neuropathy: peripheral neuropathy (<1–83.7%, grade 3/4 0–5%), peripheral sensory neuropathy (<1–18%, grade 3/4 0–2%), general neuropathy (0–14%, grade 3/4 0–2%), dysgeusia (4–13%, grade 3/4 <1%), dysesthesia (0–13%, grade 3/4 0–3%), headache (5–12%, grade 3/4 <1%), dizziness (11%).

Common: insomnia, lethargy, hypoesthesia, hyperesthesia, polyneuropathy, tremor. In most cases paresthesia occurred in association with hand-foot syndrome.

Uncommon: encephalopathy, confusion, cerebellar signs such as ataxia, dysarthria, impaired balance and abnormal coordination.

Frequency not known: toxic leukoencephalopathy has been observed in the postmarketing setting.

Eyes

Very common, mostly in combination with docetaxel: increased tear secretion (<1-12%)

Common: conjunctivitis, eye irritation, blurred vision.

Very rare: lacrimal duct stenosis and corneal disorders including keratitis have been observed in the postmarketing phase.

Heart

Common: cardiac ischemia/infarction, palpitations (in combination with Herceptin + cisplatin).
Uncommon: heart failure, cardiomyopathy, sudden cardiac death, tachycardia, atrial arrhythmias including atrial fibrillation, ventricular extrasystoles.

Vessels

Very common: hypertension (mainly in combination with bevacizumab): <1–12%, grade 3/4 <1–3%), lower limb edema (mainly in combination with docetaxel: 4–14%), thromboembolism (13.3%, mainly in combination with cisplatin plus epirubicin).

Common: hypotension (in combination with Herceptin + cisplatin).

Respiratory organs

Very common: pharyngeal dysesthesia (0–13%, grade 3/4 0–2 %), sore throat (mainly in combination with docetaxel: <1–11%, grade 3/4 2%), singultus (12%, in combination with Herceptin + cisplatin).

Common: dyspnea, epistaxis, cough, pharyngolaryngeal and oropharyngeal pain, rhinorrhea, dysphonia, pulmonary embolism (in combination with cisplatin).

Gastrointestinal disturbances

Very common: diarrhea (23–64%, grade 3/4 5–22%), nausea (33–82.1%, grade 3/4 2–11.4%), vomiting (14–82.1%, grade 3/4 2–11.4%), stomatitis (12–39.1%, grade 3/4 <1–4%, in combination with docetaxel: 67%, grade 3/4 18%), abdominal pain (10–25%, grade 3/4 2–7%), constipation (6–20%, grade 3/4 <1–1%), dyspepsia (6–12%, grade 3/4: <1%).

Common: epigastric discomfort, abdominal distension, dry mouth, flatulence, oral pain, gastritis, dysphagia, gastrointestinal hemorrhage (in combination with Herceptin + cisplatin).

Uncommon: esophagitis, duodenitis, colitis.

Rare: intestinal obstruction.

Hepatobiliary

Very common: elevation in ASAT (25.1–28.7%; grade 3/4 0.3–07%), ALAT (16.7–27.2%; grade 3/4 0.4–1.3%), bilirubin (1–50.3%; grade 3/4 15.3–18.6%), alkaline phosphatase (26–27.2%; grade 3/4 0–0.1%).

Very rare: hepatic impairment, cholestatic hepatitis.

Skin

Very common: hand-foot syndrome or palmar-plantar erythrodysesthesia (22–63%, grade 3/4 4–24%), dermatitis (<1–10%, grade 3/4 <1%), nail changes (1–14%, grade 3/4 0–2%; e.g. nail discoloration, onycholysis), alopecia (mainly in combination with docetaxel or cisplatin with or without epirubicin: 1–82.5%, grade 3/4 0–47.4%).

Common: dry skin, rash, erythema, pigmentation disturbances, pruritus, localized exfoliation, skin fissures.

Uncommon: photosensitivity reactions, radiation recall phenomenon, exfoliative dermatitis, itchy erythema, brittle nails, nail dystrophy.

Very rare: cutaneous lupus erythematosus, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been observed in the postmarketing setting.

Musculoskeletal system

Very common: pain in the limbs (mostly in combination with oxaliplatin: 0–12%, grade 3/4 <1%), myalgia (1–14%, grade 3/4 2%), arthralgia (<1–11%, grade 3/4 1%), all mostly in combination with docetaxel.

Common: limb pain, back pain, rigor, pain in jaw, muscle weakness.

Kidneys and urinary tract

Very common: elevation in serum creatinine (9.8–18%, grade 3/4 0–0.4%).

Rare: acute renal failure secondary to dehydration, sometimes with fatal outcome, has been observed in the postmarketing setting.

Reproductive system and breast

Uncommon: breast pain.

Ear and inner ear

Common: tinnitus, hypoacusis (both in combination with Herceptin + cisplatin), vertigo.

General disorders

Very common: exhaustion (15–24%, grade 3/4 0–3%), fever (4–21%, grade 3/4 1%), asthenia (4–23%, grade 3/4 <1–7%), fatigue (17–38%, grade 3/4 2–7%, in combination with cisplatin or oxaliplatin with or without epirubicin: 15–96.1%, grade 3/4 <1–24.9%), temperature intolerance (5–11%), weight loss (in up to 23% in combination with cisplatin), pyrexia (in up to 20% in combination with Herceptin + cisplatin), edema (10%).

Common: fever, malaise, pain.

OVERDOSAGE

The symptoms of acute overdose are nausea, vomiting, diarrhea, inflammation of mucous membranes, gastrointestinal irritation, bleeding, and bone marrow aplasia. Clinical treatment of overdose must include customary therapeutic and supportive clinical

interventions aimed at eliminating the existing clinical symptoms and preventing possible complications.

PROPERTIES AND EFFECTS

ATC code: L01BC06

Mechanism of action/pharmacodynamics

Capecitabine is a fluoropyrimidine carbamate for oral use and belongs to the group of tumor-activated and tumor-selective cytostatics. It is not itself cytotoxic, but is converted by three enzymatic steps, the final step preferentially in the tumor, into the cytotoxic active substance 5-FU.

5-FU inhibits cell division by blocking DNA synthesis (enzyme inhibition), resulting in the formation of structurally defective RNA (incorporation of 5-FU), which directly affects protein biosynthesis.

The formation of 5-FU from capecitabine is preferentially catalyzed in the tumor by the tumor-associated angiogenic factor thymidine phosphorylase. This keeps the burden on healthy tissue, due to systemic 5-FU, to a minimum. The stepwise enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations in tumor tissue than in normal tissue.

After oral administration of capecitabine to patients with colorectal cancer (n=8) the ratio between the 5-FU concentration in the tumor and the concentration in the surrounding tissue was 3.2 (between 0.9 and 8.0). The ratio between the 5-FU concentration in the tumor and plasma concentration was 21.4 (between 3.9 and 59.9), whereas the ratio between healthy tissue and plasma was 8.9 (between 3.0 and 25.8). The thymidine phosphorylase concentration was determined and found to be around four times higher in primary colon tumors than in the surrounding normal tissue.

Other studies have shown that the thymidine phosphorylase concentration is higher too in other human tumors such as breast, stomach, cervical and ovarian cancer than in the surrounding tissue.

Clinical efficacy

Monotherapy in adjuvant colon cancer
In a study, 1004 patients were treated with Xeloda (3-week cycles for 24 weeks, with 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period), and 983 patients with 5-FU and leucovorin (5-FU/LV, Mayo regimen for 24 weeks). In the intent-to-treat (ITT) population, Xeloda was equivalent to 5-FU/LV in the primary endpoint of disease-free survival (HR [PP] 0.87 [0.76–1.00]). There was no significant difference in overall survival (HR [PP] 0.88 [0.74–1.05]). At the time of the analysis the median follow-up was 4.4 years. A further analysis after a median 6.9 years produced similar results.

Combination therapy in adjuvant colon cancer

Data from one multicenter, randomized, controlled phase III clinical trial in patients with stage III (Dukes' C) colon cancer support 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 randomized 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) (XELOX), and 942 patients to bolus 5-FU and leucovorin (5-FU/LV).

In the primary analysis for disease-free survival (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 hazard ratio of 0.78 (95% CI=[0.67; 0.92]; p=0.0024) for XELOX vs. 5-FU/LV.

XELOX showed a trend towards superior overall survival (OS) with a hazard ratio of 0.87 (95% CI=[0.72; 1.05]; p=0.1486), which was reflected in a 13% reduction in the risk of death. The 5-year OS rate was 78% for XELOX versus 74% for 5-FU/LV. The efficacy data are based on a median observation time of 59 months for OS and 57 months for DFS. In the ITT population the rate of withdrawal due to adverse events was higher in the XELOX combination therapy arm (21%) than in the 5-FU/LV monotherapy arm (9%).

After a median follow-up of 7 years, the statistically significantly superior DFS (HR=0.80, 95% CI 0.69, 0.93; p=0.0038) and RFS (HR=0.78, 95% CI 0.67, 0.91; p=0.0015) were maintained on XELODA. The 7-year OS rate was 73% in the XELOX arm and 67% in the 5-FU/LV arm. In the two additional years of follow-up after the primary analysis, the difference between the survival rates increased from 3% to 6%.

Monotherapy – First-line therapy with Xeloda in metastatic colorectal cancer

In two studies, a total of 603 patients were treated with Xeloda (3-week cycles of 1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period) and 604 patients were treated with 5-FU and leucovorin (Mayo regimen). The objective overall response rate in the total randomized population was 25.7% (Xeloda) vs. 16.7% (Mayo regimen), p<0.0002. The average time to progression of the disease was 140 days (Xeloda) vs. 144 days (Mayo regimen). Average survival was 392 days (Xeloda) vs. 391 days (Mayo regimen).

Combination therapy – First-line therapy of metastatic colorectal cancer

In a randomized multicenter study (NO16966) performed in a total of 2035 patients, XELOX and FOLFOX-4 were found to be therapeutically equivalent in terms of progression-free and overall survival. A pre-specified primary exploratory analysis showed the treatment subgroup XELOX + bevacizumab to be equivalent to the treatment

subgroup FOLFOX-4 + bevacizumab in terms of median progression-free survival (hazard ratio 1.01 [97.5% CI 0.84–1.22]). The median follow-up period at the time of the primary analysis in the intent-to-treat population was 1.5 years.

In a randomized multicenter study (NO16967) performed in a total of 627 patients with metastatic colorectal cancer who had previously received irinotecan and a fluoro-pyrimidine-containing regimen as first-line therapy, no significant differences were found between XELOX and FOLFOX-4 in terms of progression-free or overall survival. The median follow-up period at the time of the primary analysis in the intent-to-treat population was 2.1 years.

Combination therapy – Therapy with Xeloda and docetaxel in locally advanced or metastatic breast cancer

In a phase III study, 255 patients were treated with Xeloda (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week treatment break) plus docetaxel (75 mg/m^2 as a 1-hour intravenous infusion every 3 weeks) after failure of an anthracycline-containing chemotherapy regimen. 256 patients received docetaxel alone (100 mg/m^2 as a 1-hour intravenous infusion every 3 weeks). The survival rate on combination therapy with Xeloda + docetaxel was significantly higher (442 days vs. 352 days with docetaxel alone; p=0.0126). The overall response rate in the all-randomized population (investigator assessment) was 41.6% on Xeloda + docetaxel vs. 29.7% on docetaxel alone (p=0.0058). The median time to disease progression or death on Xeloda + docetaxel (186 days) was significantly longer (p<0.0001) than with docetaxel alone (128 days).

Treatment of locally advanced or metastatic breast cancer with Xeloda and vinorelbine

The combination was evaluated in a total of four phase II studies involving 262 female patients. In all studies the patients received Xeloda 1000 mg/m^2 twice daily for 14 days, followed by a 7-day rest period. Vinorelbine was administered to 92 patients at a dose of 60 mg/m^2 orally on days 1, 8 and 15, to 115 patients at a dose of 60 mg/m^2 orally on days 1 and 8, and to 55 patients at 60 mg/m^2 orally on days 1 and 8 of the first cycle and 80 mg/m^2 orally on days 1 and 8 of all subsequent cycles.

Response rates of between 20% and 56.5% (ITT) and between 23.5% and 56.5% (PPT) were found. Median progression-free survival was 3.4, 8.4, 8.4 and 10.5 months, and median overall survival 11.3, 17.5, 25.8 and 29.2 months.

Monotherapy – Treatment of locally advanced or metastatic breast cancer with Xeloda (after earlier treatment with taxanes and anthracyclines or when anthracyclines are contraindicated)

In two phase II studies a total of 236 female patients were treated with Xeloda (1250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period). The response rates were 20% (first study) and 25% (second study). The average time to progression of the disease was 93 and 98 days and average survival was 384 and 373 days.

Combination therapy – Esophageal cancer, cancer of the gastroesophageal junction and gastric cancer

In a randomized 4-arm phase III study (REAL-2), 1002 patients with advanced or metastatic esophageal cancer, cancer of the gastroesophageal junction or gastric cancer were treated with one of the four following triple combinations: EOX = epirubicin (50 mg/m^2 as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m^2) as a two-hour infusion on day 1 every 3 weeks and capecitabine (625 mg/m^2 twice daily with no treatment break) or EOF = epirubicin and oxaliplatin with 5-FU (200 mg/m^2 daily as a continuous infusion) or ECX = epirubicin, cisplatin (60 mg/m^2) as a two-hour infusion on day 1 every 3 weeks and capecitabine (625 mg/m^2 twice daily with no treatment break) or ECF = epirubicin, cisplatin with 5-FU (200 mg/m^2 daily as a continuous infusion).

With regard to the primary endpoint of overall survival, primary efficacy analysis in the per-protocol population showed noninferiority for capecitabine- vs. 5-FU-based arms (hazard ratio 0.86, 95% CI 0.80–0.99) and for oxaliplatin- vs. cisplatin-based arms (hazard ratio 0.92, 95% CI 0.80–1.05). Median overall survival of the per-protocol population was 10.9 months in the capecitabine-based arms vs. 9.6 months in the 5-FU-based arms, and 10.0 months in the cisplatin-based arms vs. 10.4 months in the oxaliplatin-based arms.

Median overall survival was 11.2 vs. 9.3 months on EOX vs. EOF and 9.9 vs. 9.9 months on ECX vs. ECF. Median progression-free survival was 7.0 (EOX), 6.5 (EOF), 6.7 (ECX) and 6.2 (ECF) months, with corresponding response rates of 47.9%, 42.4%, 46.4% and 40.7%.

Combination therapy – Adenocarcinoma of the stomach or gastroesophageal junction

With regard to combination with Herceptin and cisplatin (ToGA study), see the prescribing information for Herceptin.

PHARMACOKINETICS

The pharmacokinetics of capecitabine have been evaluated over a dose range of 502–3514 mg/m^2/day. The parameters of capecitabine and the metabolites 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5-fluorouridine (5'-DFUR) measured on days 1 and 14 were similar. The AUC of 5-FU was 30%–35% higher on day 14, but did not increase subsequently (day 22). At therapeutic doses, the pharmacokinetics of capecitabine and its metabolites were dose-proportional, except for 5-FU.

Absorption

Orally administered capecitabine is rapidly and completely absorbed through the intestinal mucosa as the intact molecule. This is followed by rapid metabolization. Administration with food decreases the rate of capecitabine absorption, but has only a slight effect on the area under the curve (AUC) of 5'-DFUR, and on the AUC of the subsequent metabolite 5-FU.

After a dose of 1250 mg/m^2 on day 14 (taken with food), the peak plasma concentrations (C_{max} in µg/ml) for capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and a-fluoro-b-alanine (FBAL, metabolite of 5-FU) were 4.47, 3.05, 12.1, 0.95 and 5.46 respectively. The time to peak plasma concentration (T_{max} in h) was 1.50, 2.00, 2.00, 2.00 and 3.34. The

$AUC_{0-¥}$ values in µg•h/ml were 7.75, 7.24, 24.6, 2.03 and 36.3. The plasma AUC for 5-FU after administration of capecitabine is some 6–22 times lower than after an intravenous bolus of 5-FU (dose: 600 mg/m^2).

Distribution

In vitro studies with human plasma have shown that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are respectively 54%, 10%, 62% and 10% bound to protein, principally albumin.

Metabolism

Capecitabine is first metabolized by hepatic carboxylesterases to 5'-deoxy-5-fluoro-cytidine (5'-DFCR). This is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase, which is principally located in the liver and tumor tissues. Further catalytic activation of 5'-DFUR to 5-FU, mediated by thymidine phosphorylase, takes place primarily in the tumor tissue and in the liver.

Except for 5-FU, no cytotoxicity was demonstrated *in vitro* for the metabolites of capecitabine.

5-FU is further catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD) to the much less toxic dihydro-5-fluorouracil (FUH2). The dihydropyrimidinase enzyme cleaves the pyrimidine ring to form 5-fluoro-ureidopropionic acid (FUPA). Finally, b-ureido-propionase cleaves FUPA to a-fluoro-b-alanine (FBAL), which is excreted in the urine. Dihydropyrimidine dehydrogenase (DPD) activity is the rate-limiting step. Deficiency in DPD can result in increased toxicity of capecitabine (see *Contraindications* and *Warnings and precautions*).

Elimination

The elimination half-life of capecitabine and its metabolites 5'-DFCR, 5'-DFUR, 5-FU and FBAL is 0.85, 1.11, 0.66, 0.76 and 3.23 respectively. The capecitabine metabolites are for the most part excreted in urine (95.5% of the administered dose): capecitabine (2.9%), 5'-DFCR (7.2%), 5'-DFUR (11.1%), 5-FU (0.54%) and FBAL (57%). Fecal excretion is minimal (2.6%).

Pharmacokinetics in special patient populations

Patients with hepatic impairment due to liver metastases

No clinically relevant effects on the bioactivation or pharmacokinetics of capecitabine were observed in cancer patients with mild to moderate hepatic impairment due to liver metastases (see *Dosage and administration*).

No pharmacokinetic data are available on patients with severe hepatic impairment.

Patients with renal impairment

In a pharmacokinetic study in cancer patients with mild to severe renal impairment, there was no evidence of any effect of creatinine clearance on the pharmacokinetics of the intact substance or 5-FU. It was observed that creatinine clearance influences the

systemic availability of 5'-DFUR (35% increase in AUC in association with a 50% reduction in creatinine clearance) and of FBAL (114% increase in AUC in association with a 50% reduction in creatinine clearance). The metabolite FBAL has no anti-proliferative activity.

Elderly patients

Based on the population pharmacokinetic analysis, which included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients aged at least 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 probably due to a change in renal function (see *Patients with renal impairment*).

Children

There are no data on the pharmacokinetics in children.

Kinetics in special populations

A population pharmacokinetic analysis was carried out after Xeloda treatment of 505 patients with colorectal cancer dosed at 1250 mg/m^2 twice daily. Gender, presence or absence of liver metastases at the start of treatment, Karnofsky index, total bilirubin, serum albumin, ASAT and ALAT had no statistically significant influence on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL.

PRECLINICAL DATA

Reproduction

The administration of capecitabine to female mice resulted in impaired fertility; in a 13-week study in male mice, atrophic and degenerative changes to the reproductive organs were observed. In both cases the findings were reversible after a treatment-free interval.

Like other fluoropyrimidines, capecitabine also showed embryolethal and teratogenic effects (class effect).

Mutagenicity

Capecitabine was not mutagenic *in vitro* in bacteria (Ames test) or mammalian cells (V79/HPRT) or *in vivo* in the mouse micronucleus test. However, like other nucleoside analogues, capecitabine was clastogenic in human lymphocytes under *in vitro* conditions.

SPECIAL REMARKS

Stability

This medicine should not be used after the expiry date (EXP) shown on the pack.

Special precautions for storage

Do not store above 30°C.

Disposal instructions

Any medicinal products unused after the end of treatment or by the expiry date should be returned in their original packaging to the place of supply (physician or pharmacist) for proper disposal.

Packs

Tablets 150 mg	60
Tablets 500 mg	120

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

Council of Arab Health Ministers

Union of Arab Pharmacists

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