DIROGIT®

Capecitabine

COMPOSITION

Active ingredient: capecitabine.

INDICATIONS AND POTENTIAL USES

Adjuvant treatment of patients with colon cancer (Dukes' stage C) in whom monotherapy with fluoropyrimidines is indicated. 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). Second line therapy in combination with docetaxel in patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy with anthracyclines. Third-line therapy in patients with locally advanced or metastatic breast cancer after failure of paclitaxel and chemotherapy with anthracyclines. 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.

DOSAGE AND ADMINISTRATION

Normal dosage

Dirogit tablets are to be taken with water within 30 minutes after a meal.

Monotherapy

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

In combination with docetaxel

In combination with docetaxel, the recommended dose of Dirogit is 1250 mg/m² twice daily for 14 days followed by a 7-day rest period, combined with docetaxel 75 mg/m² 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 oxaliplatin

Following administration of oxaliplatin as a 130 mg/m² intravenous infusion over 2 hours, treatment with Dirogit 1000 mg/m² 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 Dirogit as described in the combination with oxaliplatin section. For detailed information, please refer to the prescribing information for Bevacizumab. The following tables show how the standard dose and the reduced dose of Dirogit (see Dosage adjustment during treatment) are calculated for a 1250 mg/m² or 1000 mg/m² starting dose of Dirogit.

In combination with oxaliplatin and epirubicin

The recommended dose of Dirogit is 625 mg/m² twice weekly with no treatment break for 24 weeks in combination with oxaliplatin 130 mg/m² (every 3 weeks) and epirubicin 50 mg/m² (every 3 weeks). For detailed information on premedication to maintain adequate hydration and antiemesis before oxaliplatin administration, see the prescribing information on oxaliplatin.

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

Dose level 1250 mg/m² (twice daily)

	Full dose 1250 mg/m²	Number of 500 mg tablets and / or 150 mg 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
> 2.19	2800	2	5	2150	1450

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

Dose level 1000 mg/m² (twice daily)

	Full dose 1000 mg/m²	Number of 500 mg tablets and / or 150 mg 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	900
1.79-1.92	1800	2	3	1400	800
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 adjustment during treatment

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

Patients taking Dirogit should be informed of the need to interrupt treatment immediately if moderate or severe side effects occur. Doses of Dirogit 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 Dirogit

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 patients 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 x10⁹/L and/or platelet counts of < 100 x 10⁹/L should not be treated with Dirogit. If laboratory assessments during a treatment cycle show grade 3 or 4 hematological toxicity treatment with Dirogit should be interrupted until the toxicity has resolved to grade 0-1.

Special dosage instructions

Hepatic impairment: The pharmacokinetics of Dirogit 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 Dirogit should be interrupted if treatment-related elevations in bilirubin of >3.0 xULN (upper limit of normal) or treatment-related elevations in hepatic aminotransferases (ALAT, ASAT) of > 2.5 x ULN occur. Treatment with Dirogit may be resumed when bilirubin decreases to < 3.0 xULN or hepatic aminotransferases decrease to < 2.5 xULN. 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), Dirogit is contraindicated.

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 Dirogit should be reduced to 75% of the recommended starting dose. In patients with severe renal impairment (creatinine clearance < 30 ml/min) Dirogit is contraindicated. If the calculated creatinine clearance falls to < 30 ml/min during-treatment, Dirogit should be stopped.

Children and adolescents (under 18 years): No studies have been performed on the tolerability and efficacy of Dirogit 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 Dirogit monotherapy or combination with oxaliplatin, but careful monitoring is advised. In combination with docetaxel it is recommended that the Dirogit 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 dihydropyrimidine dehydrogenase (DPD) deficiency.

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.

WARNINGS AND PRECAUTIONS

Dirogit should be prescribed only by a suitably qualified doctor with experience in the use of antineoplastic drugs.

Since Dirogit 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 Dirogit 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.

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. If grade 2 or higher dehydration occurs, Capecitabine 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.

Hand-foot syndrome: Capecitabine can cause hand-foot syndrome (palmarplantar erythrodysesthesia or chemotherapy induced acral erythema) with a severity of between 1 and 3. In patients on Capecitabine 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 for 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 Capecitabine dose should be adjusted.

The occurrence, in rare cases, of unexpected severe side effects (e. g. stomatitis, diarrhea, neutropenia, possibly associated with fever and neurotoxicity) during treatment with 5-FU has been attributed to reduced dihydropyrimidine dehydrogenase (DPD) activity. A connection between DPD deficiency and increased side effects of capecitabine cannot therefore be ruled out. 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, Capecitabine should be used with caution. Capecitabine 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 Capecitabine should be reduced to 75% of the recommended starting dose.

The cardiotoxic side effects observed during treatment with Capecitabine, 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 tumors with Capecitabine 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.

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

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, Capecitabine 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 Capecitabine with phenytoin. Patients taking phenytoin concomitantly with Capecitabine should be regularly monitored for increased plasma phenytoin concentrations and associated clinical symptoms.

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

Antacids: Ingestion of Capecitabine 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'-DFDR, 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 Capecitabine 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 Capecitabine 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/m² per day, whereas it is only 2000 mg/m² 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 Capecitabine 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 Dirogit during pregnancy may damage the fetus. The substance should be regarded as teratogenic in humans. Dirogit should not be used during pregnancy.

If Dirogit 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 Dirogit. Women and men receiving treatment with Dirogit should employ contraceptive measures. It is not known whether Dirogit is excreted in breast milk. In a study in which, suckling mice were given a single oral dose of Capecitabine, significant amounts of capecitabine metabolites were detected in milk. Breastfeeding should therefore be avoided during treatment with Capecitabine.

Effects on ability to drive and use machines

Dirogit 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 handfoot syndrome (palmar-plantar erythrodysesthesia).

The undesirable effects of the combination of Capecitabine with oxaliplatin and/or bevacizumab correspond to the undesirable effects that have been reported with Capecitabine or oxaliplatin monotherapy or bevacizumab combination therapy.

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
Common: Herpes simplex infections, rhinopharyngitis, oral candidiasis.
Rare: Local and lethal systemic infections (bacterial, viral or fungal etiology), sepsis.
Immunsystem
Common, mostly in combination with oxaliplatin: hypersensitivity reactions.
Blood and lymphatic system
Very common: lymphocytopenia (51.3-56.2%, 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 52.9%, in combination with cisplatin with or without epirubicin: 33-85.6%, grade 3/4 18-51.1%), febrile neutropenia (mainly in combination with docetaxel and cisplatin with or without epirubicin: 10.5-16%, grade 3/4 6.7%), leukopenia (14%, grade 3/4 3%).
Common: granulocytopenia.
Uncommon: pancytopenia, bone marrow depression.
Metabolism and nutrition disorders
Very common: anorexia, (9-31 %, grade 3/4 3%), hyperglycemia (40%, grade 3/4 0.9%), hypocalcemia (13.2%, grade 3/4 0.8%), hyponatremia (17.5%, grade 3/4 0.4-1%), reduced appetite (5-10%).
Common: hypercalcemia, hypokalemia, dehydration, weight loss.
Psychiatric disturbances
Common: Depression.
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 (5-37%, grade 3/4 0-6%); peripheral neuropathy (<1-83.7%, grade 3/4 0-5%), peripheral sensory neuropathy (<1-18%, grade 3/4 0-2%), dysgeusia (4-12%, grade 3/4 <1%), neuropathy (0-14%, grade 3/4 0-2%), dysesthesia (0-13%, grade 3/4 0-3%), headache (5-12%, grade 3/4 <1%), dizziness (10%).
Common: insomnia, lethargy, hypoesthesia, hyperesthesia. Most cases of paresthesia have occurred in association with the hand-foot syndrome.
Uncommon: Encephalopathy, confusion, cerebellar symptoms such as ataxia, dysarthria, impaired balance and abnormal coordination.
Eyes
Very common, mostly in combination with docetaxel: increased tear secretion (12%).
Common: conjunctivitis, eye irritation, blurred vision.
Very rare: Lacrimal duct stenosis has been observed in the post marketing phase.
Heart
Common: myocardial ischemia/infarction.
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 combinatin with cisplatin plus epirubicin).
Respiratory organs
Very common: pharyngeal dysesthesia (0-13%, grade 3/4 0-2%), sore throat (mostly in combination with docetaxel: 11%, grade 3/4 2%).
Common: dyspnea, epistaxis, cough, pharyngolaryngeal pain, rhinorrhea, dysphonia.
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 (6-16%, grade 3/4 < 1-1 %), dyspepsia (6-12%, grade 3/4: <1%).
Common: upper abdominal pain, mouth dryness, flatulence, oral pain, gastritis, malaise.
Uncommon: esophagitis, duodenitis, colitis, gastrointestinal bleeding.
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 (36.9-50.3%; 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 discolouration, onycholysis), alopecia (mainly in combination with docetaxel or cisplatin with or without epirubicin: 1-82.1%, 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.
Musculoskeletal system
Very common: pain in the limbs (mostly in combination with oxaliplatin: 0-10%, grade 3/4 < 1%), myalgia (14%, grade 3/4 2%), arthralgia (11%, grade 3/4 1%), all mostly in combination with docetaxel.
Common: limb pain, back pain, rigor, pain in jaw.
Kidneys and urinary tract
Very common: Elevation in serum creatinine (9.8-13.8%, grade 3/4 0-0.4%).
Reproductive system and breast
Uncommon: Breast pain.
Ear and inner ear
Common: vertigo.
General disorders
Very common: exhaustion (15-24 %, grade 3/4 0-3%), pyrexia (4-21%, grade 3/4 1%), asthenia (4-23%, grade 3/4 <1-7%), fatigue (17-36%, grade 3/4 2-7%, in combination with cisplatin or oxaliplatin with or without epirubicin: 15-96.1%, grade 3/4 < 1-24.9%).
Common: Pyrexia, malaise, pain, heat intolerance, lethargy.

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 controlling the presenting clinical symptoms and preventing possible complications.

PROPERTIES AND EFFECTS
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-F-U 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 catalysed 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 then ,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
Adjuvant therapy with Capecitabine in colon cancer In a study, 1004 patients were treated with capecitabine (3-week cycles for 24 weeks, with 1250 mg/m² twice daily for 2 weeks followed by a 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, capecitabine 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.
Monotherapy - First-line therapy with Capecitabine in metastatic colorectal cancer in two studies, a total of 603 patients were treated with capecitabine (3-week cycles of 1250 mg/m² twice daily for 2 weeks followed by a 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% (capecitabine) vs. 16.7% (Mayo regimen), p<0.0002. The average time to progression of the disease was 140 days (capecitabine) vs.144 days (Mayo regimen). Average survival was 392 days (capecitabine) vs. 391 days (Mayo regimen).
Combination therapy - First line therapy of metastatic colorectal cancer in a randomized multicentric study (N016966) 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 multicentric study (N016967) performed in a total of 627 patients with metastatic colorectal cancer who had previously received irinotecan and a fluoropyrimidine-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 - Second-line therapy with Capecitabine and docetaxel in locally advanced or metastatic breast cancer. In a phase III study, 255 patients were treated with capecitabine (1250 mg/ m² twice daily for 2 weeks followed by a one week treatment break) plus docetaxel (75 mg/m² as an 1 hour intravenous infusion every 3 weeks) after failure of an anthracycline-containing chemotherapy regimen.
256 patients received docetaxel alone (100 mg/m² as an 1 hour intravenous infusion every 3 weeks). The survival rate on combination therapy with capecitabine + 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 41.8% on capecitabine + docetaxel vs. 29.7% on docetaxel alone (p = 0.0058).
The median time to disease progression or death on capecitabine + docetaxel (186 days) was significantly longer (p < 0.0001) than with docetaxel alone (128 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/m² as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m²) as a two-hour infusion on day 1 every 3 weeks and capecitabine (625 mg/m² twice daily with no treatment break) or EOF = epirubicin and oxaliplatin with 5-FU (200 mg/m² daily as a continuous infusion) or ECX = epirubicin, cisplatin (60 mg/m²) as a two-hour infusion on day 1 every 3 weeks and capecitabine 625 mg/m² twice daily with no treatment break) or ECF = epirubicin, cisplatin with 5-FU (200 mg/m² daily as a continuous infusion). With regard to the primary endpoint of overall survival, primary efficacy analysis in the per-protocol population showed non-inferiority 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%.
Monotherapy - Third line therapy with Capecitabine in locally advanced or metastatic. Breast cancer (after earlier treatment with taxanes and anthracyclines or when anthracyclines are contraindicated)
In two phase III studies, a total of 236 female patients were treated with capecitabine (1250 mg/m² twice daily for 2 weeks followed by a 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.

PHARMACOKINETICS
The pharmacokinetics of capecitabine have been evaluated over a dose range of 502-3514 mg/m²/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 metabolism. 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/m² on day 14 (taken with food), the peak plasma concentrations, (C_{max} in µg/ml) for capecitabine 5'-DFCR, 5'-DFUR, 5-FU ,and α-fluoro β-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 $AUC_{0\infty}$ - 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/m²).
Distribution
In vitro studies with human plasma have shown that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are respectively 64%, 10%, 62% and 10% bound to protein, principally albumin.
Metabolism
Capecitabine is first metabolised by hepatic carboxylesterases to 5'-deoxy-5-fluorocytidine (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 toxic dihydro-5-fluorouracil (FUH2). The dihydropyrimidinase enzyme cleaves the pyrimidine ring to form 5'-fluoro-uredopropionic acid (FUPA). Finally, β-ureidopropionase cleaves FUPA to α-fluoro β-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.
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 hour 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.
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 antiproliferative 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.
Children
There are no data on the pharmacokinetics in children.
Kinetics in special populations
A population pharmacokinetic analysis was carried out after Capecitabine treatment of 505 patients with colorectal cancer dosed at 1250 mg/m² 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.

STORAGE CONDITIONS
Store Below 30°C.

PRESENTATION
Film Coated Tablets
DIROGIT 150 mg: Capecitabine 150 mg/ Film Coated Tablet
DIROGIT 500 mg: Capecitabine 500 mg/ Film Coated Tablet
Excipients: Lactose anhydrous, microcrystalline cellulose 101, croscarmellose sodium, hypromellose (methocel E5 2910), magnesium stearate.
Film coating: opadry II pink (hypromellose, talc, titanium dioxide, ferric oxide red and ferric oxide yellow).

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, 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.

Manufactured by: The Arab Pharmaceutical Manufacturing Co. Ltd., Sahab - Jordan
For HIKMA Pharmaceuticals, Amman - Jordan

Keep medicament out of the reach of children
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