

CAPETERO 150 (Capecitabine Film-Coated Tablet 150mg) CAPETERO 500 (Capecitabine Film-Coated Tablet 500mg)

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1. NAME OF THE MEDICINAL PRODUCT

CAPETERO 150 (Capecitabine Film-Coated Tablet 150mg)
CAPETERO 500 (Capecitabine Film-Coated Tablet 500mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CAPETERO 150: Each film-coated tablet contains 500mg Capecitabine.
Excipient with known effect: Each film-coated tablet contains 11.520 mg of Anhydrous lactose

CAPETERO 500: Each film-coated tablet contains 500mg Capecitabine.
Excipient with known effect: Each film-coated tablet contains 38.400 mg of Anhydrous lactose

3. PHARMACEUTICAL FORM

Film-coated tablets

3.1 Product description

CAPETERO 150: Light peach colored, 11.4 mm x 5.4 mm capsule shaped, biconvex, film coated tablets debossed with 'S' on one side and 'H' on the other side.
CAPETERO 500: Peach colored, 15.9 mm x 8.4 mm oval shaped, biconvex, film coated tablets debossed with '3' on one side and 'H' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Breast Cancer

Capecitabine 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. Capecitabine 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. Capecitabine is indicated in combination with lapatinib ditosylate for the treatment of patients with advanced or metastatic breast cancer whose tumors over express HER2 and who have received prior therapy including an anthracycline, a taxane and trastuzumab.

Colon, Colorectal cancer

Capecitabine is indicated for the treatment of patients with metastatic colorectal carcinoma. Capecitabine is indicated as adjuvant treatment of patients following surgery of Stage III (Duke's Stage C) colon cancer.

Oesophagogastric Cancer

Capecitabine is indicated as first line treatment of patients with advanced oesophagogastric cancer in combination with a platinum based regimen.

4.2 Posology and method of administration

Standard dosage

Capecitabine tablets should be swallowed whole with water within 30 minutes after a meal. Capecitabine tablets should not be crushed or cut. If patients cannot swallow capecitabine tablets whole and tablets must be crushed or cut, this should be done by a professional trained in the safe handling of cytotoxic drugs.

Monotherapy

Colon, Colorectal and breast cancer

The recommended monotherapy starting dose of capecitabine is 1250 mg/m² administered twice daily (morning and evening; equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by a 7 day rest period.

Combination therapy

Breast Cancer

In combination with docetaxel

In combination with docetaxel, the recommended dose of capecitabine is 1250 mg/m² twice daily for 2 weeks followed by a 7 day rest period, combined with docetaxel at 75 mg/m² as a 1-hour intravenous infusion every 3 weeks.

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

In combination with lapatinib ditosylate

In combination with lapatinib ditosylate, the recommended dose of capecitabine is 2000 mg/m² (day administered orally in 2 doses 12 hours apart) for 14 days (Day 1-14) in a repeating 21 day cycle combined with lapatinib ditosylate 1250 mg (5 tablets) given orally once daily from Day 1-21.

Colon, colorectal cancer

In combination with oxaliplatin and/or bevacizumab

In combination with oxaliplatin and/or bevacizumab the recommended dose of capecitabine is 1000 mg/m² twice daily for 2 weeks followed by a 7 day rest period. The first dose of capecitabine is given on the evening of day 1 and the last dose is given on the morning of day 15. Given as a 3-weekly schedule, on day 1 every 3 weeks bevacizumab is administered as a 7.5 mg/kg intravenous infusion over 30-90 minutes followed by oxaliplatin administered as a 130 mg/m² intravenous infusion over 2 hours. Premedication to maintain adequate hydration and anti-emesis according to the oxaliplatin product information should be started prior to oxaliplatin administration for patients receiving the capecitabine plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

Gastric Cancer

In combination with platinum based regimens:

In combination with a platinum based compound the recommended dose of capecitabine for the treatment of advanced gastric cancer is 1000 mg/m² administered twice daily for 14 days followed by a 7 day rest period. The first dose of capecitabine should be given on the evening of day 1 and the last dose should be given on the morning of day 15. If epirubicin is added to this regimen the recommended dose of capecitabine is 625 mg/m² twice daily continuously. Epirubicin at a dose of 50 mg/m² should be given as a bolus on day 1 every 3 weeks. The platinum based compound (cisplatin at a dose of 80 mg/m² (triple regimen) 80 mg/m² (double regimen) or oxaliplatin at a dose of 130 mg/m²) should be given on day 1 as a 2 hour intravenous infusion every 3 weeks.

Premedication to maintain adequate hydration and anti-emesis according to the cisplatin/oxaliplatin summary of product characteristics should be started prior to cisplatin/oxaliplatin administration for patients receiving the capecitabine plus cisplatin/oxaliplatin combination.

Dose calculation

Capecitabine dose is calculated according to body surface area. The following tables show the standard and reduced dose calculations for a starting dose of capecitabine of either 1250 mg/m² or 1000 mg/m².

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

Body surface area (m ²)	Full dose 1250 mg/m ² Dose per administration (mg)	Dose level 1250 mg/m ² (twice daily)		Reduced dose (75%) 950 mg/m ² Dose per administration (mg)	Reduced dose (50%) 625 mg/m ² Dose per administration (mg)
		Number of tablets per administration (each administration to be given morning and evening)	150 mg		
≤ 1.26	1500	-	3	1150	800
1.27 - 1.38	1650	1	3	1200	800
1.39 - 1.52	1800	2	3	1450	950
1.53 - 1.66	2000	1	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	2	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 capecitabine of 1000 mg/m²

Body surface area (m ²)	Full dose 1000 mg/m ² Dose per administration (mg)	Dose level 1000 mg/m ² (twice daily)		Reduced dose (75%) 750 mg/m ² Dose per administration (mg)	Reduced dose (50%) 500 mg/m ² Dose per administration (mg)
		Number of tablets per administration (each administration to be given morning and evening)	150 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	1	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 capecitabine administration may be managed by symptomatic treatment and/or modification of the capecitabine dose (treatment interruption or dose reduction). Once the dose has been reduced it should not be increased or a later time. For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening treatment can be continued at the same dose without reduction or interruption.

Dosage modifications are not recommended for Grade 1 events. Therapy with capecitabine should be interrupted if a Grade 2 or 3 adverse drug reaction (ADR) occurs. Once the ADR has resolved or decreased in intensity to Grade 1, capecitabine therapy may be restarted at full dose or as adjusted according to Table 3. If a Grade 4 ADR occurs, therapy should be discontinued or interrupted until the ADR has resolved or decreased to Grade 1, and therapy should be restarted at 50% of the original dose. Patients taking capecitabine should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Doses of capecitabine omitted for toxicity are not replaced.

Haematology

Patients with baseline neutrophil counts of < 1.5 x 10⁹/l and/or thrombocyte counts of < 100 x 10⁹/l should not be treated with capecitabine. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 haematologic toxicity, treatment with capecitabine should be interrupted.

The following table shows the recommended dose modifications following toxicity related to with capecitabine:

Table 3: Capecitabine dose reduction schedule

Toxicity NCI/CTC 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	Interrupt until resolved to Grade 0/1	100%
1 st appearance		75%
2 nd appearance		50%
3 rd appearance		Not applicable
4 th appearance	Discontinue treatment permanently	Not applicable
Grade 3	Interrupt until resolved to Grade 0/1	75%
1 st appearance		50%
2 nd appearance		Not applicable
3 rd appearance	Discontinue treatment permanently	Not applicable
Grade 4	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%
1 st appearance		Not applicable
2 nd appearance	Discontinue permanently	Not applicable

*According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTC) 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 hyperbilirubinaemia. The following are the recommended dose modifications for toxicity when Capecitabine and docetaxel are used in combination:

Table 4: Capecitabine (X) in combination with docetaxel (T) dose reduction schedule

Toxicity grade ¹	Capecitabine dose changes within a treatment cycle	Recommended Dose Modifications
Grade 1	Maintain dose level	Maintain dose level
Grade 2	Interrupt until resolved (grade 0-1)	X: 100% of starting dose T: 100% (75 mg/m ²)
1 st appearance		X: 100% of starting dose T: 100% (75 mg/m ²)
2 nd appearance of same toxicity		X: 75% of starting dose T: Reduce to 55 mg/m ²
3 rd appearance of same toxicity		Interrupt until resolved (grade 0-1)
4 th appearance of same toxicity	Discontinue treatment permanently	Discontinue permanently
Grade 3	If grade 3 haematological/renal section on haematological toxicity, otherwise:	X: 75% of starting dose T: Reduce to 55 mg/m ²
1 st appearance		X: 50% of starting dose T: Discontinue permanently
2 nd appearance		Interrupt until resolved (grade 0-1)
3 rd appearance	Discontinue permanently	Discontinue permanently
Grade 4	If grade 4 haematological/renal section on haematological toxicity, otherwise:	X: Reduce to 50%
1 st appearance		T: Discontinue permanently
2 nd appearance	Discontinue permanently	Discontinue permanently

¹National Cancer Institute of Canada Common Toxicity Criteria were used except for hand-foot syndrome.

Specific dose adjustment in combination with docetaxel

Capecitabine and/or docetaxel dose modifications should be made according to the general dose modification scheme above, if nothing else is stated regarding specific dose adjustments. For those toxicities considered unlikely to become serious or life-threatening, e.g. alopecia, altered taste, nail changes, treatment can be continued at the same dose without reduction or interruption. At the beginning of a treatment cycle, if either a docetaxel or a Capecitabine treatment delay is indicated, both docetaxel and Capecitabine administration should be delayed until the requirements for restarting both drugs are met. If docetaxel has to be discontinued, Capecitabine treatment can be resumed when the requirements for restarting Capecitabine are met.

Haematology: Treatment should only be re-administered when the neutrophil count is $\geq 1.5 \times 10^9/l$ (Grade 0-1). Patients with neutropenia < 0.5 x 10⁹/l (Grade 4) for more than 1 week, or febrile (> 38°C) neutropenia, should have the docetaxel dosage reduced from 75 mg/m² to 55 mg/m². If Grade 4 neutropenia or febrile neutropenia occurs at 55 mg/m² docetaxel, docetaxel should be discontinued. Patients with baseline neutrophil counts of < 1.5 x 10⁹/l and/or thrombocyte counts of < 1.0 x 10⁹/l should not be treated with the Capecitabine/docetaxel combination.

Hypersensitivity: Patients who develop severe hypersensitivity reactions (hypotension with a decrease of ≥ 20 mm Hg, or bronchospasm, or generalized rash/erythema) should stop treatment immediately and be given appropriate therapy. These patients should not be challenged with the drug suspected to have caused hypersensitivity.

Peripheral neuropathy: For 1st appearance of Grade 2 toxicity, reduce the docetaxel dose to 55 mg/m². If Grade 3 toxicity appears, discontinue docetaxel treatment. In both instances follow the above dose modification scheme for Capecitabine.

Fluid retention: Severe (Grade 3 or 4) toxicity such as pleural effusion, pericardial effusion or ascites which are possibly related to docetaxel should be closely monitored. In case of appearance of such toxicity docetaxel treatment should be discontinued. Capecitabine treatment may be continued without dose modification.

Hepatic impairment: Docetaxel should generally not be given to patients with serum bilirubin above the upper limit of normal. The following modifications should be applied to the docetaxel dose in the event of abnormal values for ASAT, ALAT, and/or alkaline phosphatase levels:

Table 5: Modifications to the docetaxel dose.

ASAT and/or ALAT values	Alkaline phosphatase values	Docetaxel dose modification
≤ 1.5 x UNL and ≤ 5 x UNL		No dose modification
> 1.5 x UNL, ≤ 2.5 x UNL and ≤ 2.5 x UNL		No dose modification
> 2.5 x UNL, ≤ 5 x UNL and ≤ 2.5 x UNL		Reduce by 25% (not below 55mg/m ²)
> 1.5 x UNL, ≤ 5 x UNL and > 2.5 x UNL, ≤ 5 x UNL		Reduce by 25% (not below 55mg/m ²)
> 5 x UNL or > 5 x UNL (unless bone metastases are present in the absence of any liver disorder)		Delay dose by a maximum of 2 weeks. If no recovery, discontinue docetaxel.

Once the docetaxel dose is reduced for a given cycle, no further dose reduction is recommended for subsequent cycles unless worsening of the parameters is observed. In case of recovery of liver function tests after previous reduction of the docetaxel dose, the docetaxel dose can be escalated to the previous dose level.

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 occur, Capecitabine treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is hydrated and any precipitating causes have been corrected or controlled. Dose modifications applied should be those for the precipitating adverse event in accordance with the above guidelines.

Reductions to 75% and 50% of Capecitabine dose

For patients receiving Capecitabine monotherapy or Capecitabine in combination with docetaxel, the following tables show the dosage at 75% and 50%, calculated according to the body surface area:

Table 6: Calculated Capecitabine dose, reduced to 75% of the standard starting dose

Body surface area (m ²)	Dose per administration (mg)	Dose level 950 mg/m ² twice daily		Dose level 625 mg/m ² twice daily	
		150 mg	500 mg	150 mg	500 mg
≤ 1.26	1150	1	2	1	2
1.27 - 1.38	1300	2	2	2	2
1.39 - 1.52	1450	3	2	3	2
1.53 - 1.66	1600	1	3	1	3
1.67 - 1.78	1650	1	3	1	3
1.79 - 1.92	1800	2	3	2	3
1.93 - 2.06	1950	3	3	3	3
2.07 - 2.18	2000	2	4	2	4
≥ 2.19	2150	1	4	1	4

Calculated Capecitabine dose, reduced to 50% of the standard starting dose

Body surface area (m ²)	Dose per administration (mg)	Dose level 625 mg/m ² twice daily		Dose level 500 mg/m ² twice daily	
		150 mg	500 mg	150 mg	500 mg
≤ 1.26	800	2	1	2	1
1.27 - 1.38	950	3	1	3	1
1.39 - 1.52	1000	2	2	2	2
1.53 - 1.66	1150	1	2	1	2
1.67 - 1.78	1300	2	2	2	2
1.79 - 1.92	1300	2	2	2	2
1.93 - 2.06	1450	3	2	3	2
≥ 2.19	1450	2	2	2	2

Special dosage instructions

Pediatric use

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

Geriatric use

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

When Capecitabine was used in combination with other antineoplastic agents, geriatric patients (≥ 65 years) experience 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 80 years of age or more.

For patients 60 years of age or more treated with the combination of Capecitabine plus docetaxel, a starting dose reduction of Capecitabine to 75% (950 mg/m² twice daily) is recommended.

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

Renal impairment

In patients with moderate renal impairment (creatinine clearance 30 - 50 mL/min (Cockcroft and Gault)) at baseline, a dose reduction to 75% for a starting dose of 1250 mg/m² is recommended. In patients with mild renal impairment (creatinine clearance 51 - 80 mL/min), no adjustment in starting dose is recommended.

Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3, or 4 ADRs with subsequent dose adjustment as outlined in Table 3. If the calculated creatinine clearance decreases during treatment to a value below 30 mL/min, Capecitabine should be discontinued. The dose adjustment recommendations for patients with moderate renal impairment apply both to monotherapy and combination use.

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.

Patients with severe hepatic impairment have not been studied.

4.3 Contraindications

Capecitabine is contraindicated in patients with a known hypersensitivity to capecitabine or to any of its excipients.

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

Capecitabine is contraindicated in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity.

Capecitabine should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine.

Capecitabine 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.

4.4 Special warning and precautions for use

Warnings

Diarrhea: Capecitabine can induce diarrhea, which can sometimes be severe. Patients with severe diarrhea should be carefully monitored and, if they become dehydrated, should be

Gastrointestinal disorders	Constipation, Dyspepsia	Dry mouth
Skin and subcutaneous tissue disorders	Alopecia, Nail disorder	
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia, Pain in extremity	Pain in jaw, Back Pain
General disorders and administration site conditions	Pyrexia, Asthenia, Weakness, Temperature intolerance	Fever, Pain,

Frequencies based on all grades except those denoted with +, which are based on G3/4 ADR only. Hypersensitivity reactions (2%) and cardiac ischaemia/infarction (5%) have been reported commonly for Capecitabine in combination with other chemotherapy but less than 5% of patients.

Rare or uncommon ADRs reported for Capecitabine in combination with other chemotherapy are consistent with the ADRs reported for Capecitabine monotherapy or the combination product monotherapy (see prescribing information for the combination product).

Table 8: Laboratory abnormalities: CAPEFERO monotherapy in advanced colon cancer and in metastatic breast and colorectal cancer.

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

*Laboratory abnormalities were graded according to the categories of the NCI CTX Grading system. The following adverse effects have been identified during post-marketing experience with CAPEFERO 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 (≥ 1/100 to < 1/10); and uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (≥ 1/10,000 to < 1/100); unknown (cannot be estimated from the available data).

Table 7: Adverse Drug Reactions from Postmarketing Experience

System Organ Class (SOC)	Adverse Effects	Frequency
Renal and urinary disorders	Acute renal failure secondary to dehydration including fatal outcome	Rare
Nervous system disorders	Toxic leukoencephalopathy	Unknown
Hepatobiliary disorders	Hepatic failure, Cholestatic hepatitis	Very rare
Metabolism and nutrition disorders	Hypertiglyceridaemia	Unknown
Skin and subcutaneous tissue disorders	Cutaneous lupus erythematosus, Severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN)	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 Capecitabine tablets:

In the instance of exposure to crushed or cut CAPEFERO tablets, the following ADRs have been reported: eye irritation, eye swelling, skin rash, headache, paresthesia, diarrhoea, nausea, gastric irritation, and vomiting.

4.9 Symptoms and treatment of overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cytostatic (antimetabolite), ATC Code: L01BD06

Mechanism of action

Capecitabine is a fluoropyrimidine carbamate derivative, which was designed as an orally administered, tumour-activated and tumour-selective cytotoxic agent. Capecitabine is non-cytotoxic *in vitro*. However, *in vivo*, it is sequentially converted to the cytotoxic moiety, 5-Fluorouracil (5-FU), which is further metabolised.

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

The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations of 5-FU within tumour tissues. Following oral administration of capecitabine to patients with colorectal cancer (CACT Study; M66001). In this trial, 1987 patients were randomised to treatment with capecitabine (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period) and given as 3-week cycles for 24 weeks or 5-FU and leucovorin (Mayo Clinic regimen: 20 mg/m² leucovorin intravenous followed by 425 mg/m² intravenous bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks). Capecitabine was at least equivalent to intravenous 5-FU/5-FU in disease-free survival (DFS) (p = 0.0001, non-inferiority margin 1.2). In the all-randomised population, tests for difference of capecitabine vs 5-FU/5-FU in DFS and overall survival (OS) showed hazard ratios of 0.88 (95% CI 0.77-1.01; p = 0.088) 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.

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

Normal cells and tumour cells metabolise 5-FU to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor NS-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.

Clinical efficacy studies

Colon and colorectal cancer

Monotherapy with capecitabine in advanced colon cancer

Data from a multicentre, randomised, controlled phase III clinical trial in patients with stage III (Dukes' C) colon cancer supports the use of capecitabine for the adjuvant treatment of patients with colon cancer (CACT Study; M66001). In this trial, 1987 patients were randomised to treatment with capecitabine (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period) and given as 3-week cycles for 24 weeks or 5-FU and leucovorin (Mayo Clinic regimen: 20 mg/m² leucovorin intravenous followed by 425 mg/m² intravenous bolus 5-FU, on days 1 to 5, every 28 days for 24 weeks). Capecitabine was at least equivalent to intravenous 5-FU/5-FU in disease-free survival (DFS) (p = 0.0001, non-inferiority margin 1.2). In the all-randomised population, tests for difference of capecitabine vs 5-FU/5-FU in DFS and overall survival (OS) showed hazard ratios of 0.88 (95% CI 0.77-1.01; p = 0.088) 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 advanced colon cancer

Capecitabine in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer has been studied in a multicentre, randomised, controlled phase 3 clinical trial in patients with stage III (Dukes' C) colon cancer (NO16968 study). In this trial, 3443 patients were randomised to 3-week cycles for 24 weeks with capecitabine (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period) in combination with oxaliplatin (130 mg/m² intravenous infusion over 2 hours on day 1 every 3 weeks); 942 patients were randomised to bolus 5-FU and leucovorin. In the primary analysis for DFS, in the ITT population, XELOX was shown to be significantly superior to 5-FU/5-FU (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/5-FU. 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/5-FU. 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/5-FU. The efficacy data provided is based on a median observation time of 59 months for OS and 57 months for DFS.

At 17 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/5-FU 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 with capecitabine in metastatic colorectal cancer

Data from two identically designed, multicentre, randomised, controlled, phase 3 clinical trials support the use of capecitabine for first-line treatment of metastatic colorectal cancer (S014695; S014786). In these trials, 8020 patients were randomised to treatment with capecitabine (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period) and given as 3-week cycles and 804 patients were randomised to treatment with 5-FU and leucovorin (Mayo regimen: 20 mg/m² leucovorin intravenous followed by 425 mg/m² intravenous 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% (capecitabine) vs. 16.7% (Mayo regimen); p < 0.0002. The median time to progression was 140 days (capecitabine) vs. 144 days (Mayo regimen). Median survival was 392 days (capecitabine) vs. 391 days (Mayo regimen).

Combination therapy - first-line treatment of colorectal cancer
A multicentre, randomised, controlled phase 3 clinical study (NO16968) has been conducted for the use of capecitabine in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab (BV) for the first-line treatment of metastatic colorectal cancer. The study contained two parts: an initial 2-arm part in which patients were randomised to two different treatment groups, including XELOX or FOLFOX-4, and a subsequent 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 Table 8 below.

Table 8: Treatment regimens in study NO16966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + Avastin	Oxaliplatin	85 mg/m ² intravenous 2 hr	Oxaliplatin on Day 1, every 2 weeks
	Leucovorin	200 mg/m ² intravenous 2 hr	Leucovorin on Days 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m ² intravenous bolus, followed by 600 mg/m ² intravenous 22 hr	5-Fluorouracil intravenous bolus/infusion, each on Days 1 and 2, every 2 weeks
	Placebo or Avastin	5 mg/kg intravenous 3090 mins	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX + Avastin	Oxaliplatin	130 mg/m ² intravenous 2 hr	Oxaliplatin on Day 1, every 3 weeks
	Capecitabine	1000 mg/m ² oral bid	Capecitabine oral twice daily for 2 weeks (followed by 1 week off treatment)
	Placebo or Avastin	7.5 mg/kg intravenous 3090 mins	Day 1, prior to XELOX, every 3 weeks
	5-Fluorouracil: Intravenous 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 (PFS) in the eligible patient population and the intent-to-treat population. The results indicate that XELOX is equivalent to FOLFOX-4 in terms of OS. 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 PFS (hazard ratio: 1.01 [95% 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 9 below.

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

Parameter: Progression-free Survival	PRIMARY ANALYSIS			
	Population	Median Time to Event (Days)	HR (97.5% CI)	
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)
Parameter: Progression-free Survival	ADDITIONAL 1 YEAR OF FOLLOW UP			
	Population	Median Time to Event (Days)	HR (97.5% CI)	
EPP	242	259	1.02 (0.92; 1.14)	
	ITT	244	259	1.01 (0.91; 1.12)
Parameter: Overall Survival	EPP	600	584	1.00 (0.88; 1.13)
	ITT	602	586	0.99 (0.88; 1.12)

*EPP = eligible patient population; **ITT = intent-to-treat population
The CAIRO study was a randomized, controlled phase III trial to study the use of capecitabine at a starting dose of 1000 mg/m² for 2 weeks every 3 weeks in combination with irinotecan for the first-line treatment of patients with metastatic colorectal cancer. The efficacy in terms of Overall Response Rate (ORR), Progression Free Survival (PFS) and OS was similar to that reported in pivotal studies of 5-FU (Dukes' C) colon cancer (NO16968 study). In this trial, 3443 patients were randomised to 3-week cycles for 24 weeks with capecitabine (1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period) in combination with oxaliplatin (130 mg/m² intravenous infusion over 2 hours on day 1 every 3 weeks); 942 patients were randomised to bolus 5-FU and leucovorin. In the primary analysis for DFS, in the ITT population, XELOX was shown to be significantly superior to 5-FU/5-FU (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/5-FU. 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/5-FU. 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/5-FU. The efficacy data provided is based on a median observation time of 59 months for OS and 57 months for DFS.

At 17 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/5-FU 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%.

Table 10: Key non-inferiority efficacy results for the primary analysis and 6-month follow-up data of Study NO16967 (PPP and ITT populations)

Population	PRIMARY ANALYSIS			
	Median Time to Event (Days)	HR (97.5% CI)		
Parameter: Progression-free Survival	EPP	154	168	1.03 (0.87; 1.24)
	ITT	144	146	1.04 (0.83; 1.14)
Parameter: Overall Survival	EPP	388	401	1.07 (0.88; 1.31)
	ITT	383	382	1.03 (0.87; 1.23)
Population	ADDITIONAL 6 MONTHS OF FOLLOW UP			
	Median Time to Event (Days)	HR (95% CI)		
Parameter: Progression-free Survival	EPP	154	166	1.04 (0.87; 1.24)
	ITT	143	146	0.97 (0.83; 1.14)
Parameter: Overall Survival	EPP	393	402	1.05 (0.88; 1.27)
	ITT	383	382	1.02 (0.86; 1.21)

*PPP = per-protocol population; **ITT = intent-to-treat population
A pooled analysis of the efficacy data from the first-line treatment of metastatic colorectal cancer. The study contained two parts: an initial 2-arm part in which patients were randomised to two different treatment groups, including XELOX or FOLFOX-4 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 OS (hazard ratio 1.01 [95% CI: 0.87; 1.17]) with a median OS of 488 days (XELOX) versus 478 days (FOLFOX-4).

Combination therapy - Desophagoesophageal cancer

A multicentre, randomised, controlled phase 3 clinical trial (ML17032) in patients with advanced or metastatic gastric cancer studied the use of capecitabine for the first-line treatment of patients with advanced gastric cancer. In this trial, 180 patients were randomised to treatment with capecitabine (1000 mg/m² twice daily for 2 weeks followed by a 7-day rest period) and cisplatin (80 mg/m² as a 2-hour infusion every 3 weeks). A total of 156 patients were randomised to treatment with 5-FU (800 mg/m² per day, continuous infusion on days 1 to 5 every 3 weeks) and cisplatin (80 mg/m² as a 2-hour infusion on day 1, every 3 weeks). The primary objective of the study was met, capecitabine 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 (OS) was similar to the result for progression-free survival.

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

Parameter	Capecitabine/Cisplatin (N = 159)	5-FU/Cisplatin (N = 137)	Hazard Ratio (95% CI)*
Progression-free survival	5.6 (4.9, 7.2)	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 3 study (REAL-2) comparing capecitabine to 5-FU and oxaliplatin to cisplatin in patients with advanced oesophagoesophageal cancer supports the use of capecitabine for the first-line treatment of advanced oesophagoesophageal cancer. In this trial, 1002 patients were randomised in a 2x2 factorial design to one of the following 4 arms:

- ECf: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), cisplatin (80 mg/m² as a two-hour infusion on day 1 every 3 weeks) and 5-FU (200 mg/m² daily given by continuous infusion via a central line).
- ECx: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), cisplatin (80 mg/m² as a two-hour infusion on day 1 every 3 weeks), and capecitabine (625 mg/m² twice daily continuously).
- EOf: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m² given as a 2-hour infusion on day 1 every 3 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 3 weeks), and capecitabine (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 0.8-0.93) and for oxaliplatin- vs cisplatin-based regimens (hazard ratio 0.82; 95% CI 0.80-1.1). The median overall survival was 10.6 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).

Combination therapy - Gastric cancer

An open-label, randomised, multicentre (South Korea, China and Taiwan) phase 3 study (CLASSIC) comparing capecitabine plus oxaliplatin (XELOX) to observation only, following D2 resection of stage II and III gastric adenocarcinoma, was conducted for use of adjuvant XELOX for completely resected gastric cancer. Patients received oral capecitabine twice daily on a 3-week cycle consisting of 2 weeks of treatment followed by 1 week without treatment and intravenous oxaliplatin on day 1 of each cycle or observation only (no adjuvant chemotherapy). The study treatment phase was scheduled for a total of 8 cycles (24 weeks). A follow-up phase continued until date of death or the last date the patient was known to be alive, or until 2 years after the full efficacy analysis had been completed.
A total of 1025 patients were randomised into the study (ITT population: XELOX = 520, observation = 515). The primary efficacy endpoint of 3-year DFS was met at the preplanned interim analysis after 286 DFS events and following the recommendation of the IDMC (Independent Data Monitoring Committee) to fully evaluate the study. A statistically significant

benefit for the XELOX arm over the observation only arm was observed: HR = 0.58 (95% CI 0.44, 0.72, p < 0.0001). At the time of clinical cut-off a greater proportion of patients in the XELOX arm were without an event compared to patients in the observation arm: 79.6% versus 68.3%.

The HR for the secondary endpoint, OS was 0.72 (95% CI 0.52, 1.00; p = 0.0493), however as only 14% of patients reported an OS event at the time of clinical cut-off, the data are relatively immature.

The final five year follow-up DFS analysis showed almost identical results in terms of treatment effect and absolute event-free rates at 3 years HR = 0.58 (95% CI 0.47, 0.72; p < 0.0001). The HR observed for OS, at final analysis, was 0.68 (95% CI 0.51, 0.85; p = 0.015).

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

Colon, colorectal and advanced gastric cancer: meta-analysis

A meta-analysis of six clinical trials (studies S014695, S014786, M66001, NO16966, NO16967, M17032) investigated the question whether capecitabine can replace 5-FU in mono- and combination treatment in gastrointestinal cancer. The pooled analysis includes 3097 patients treated with capecitabine-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 capecitabine-containing regimens indicating that they are non-inferior to 5-FU-containing regimens.

Combination therapy - Breast cancer

Capecitabine in combination with docetaxel for treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy, including an anthracycline was studied in a multicentre, randomised, controlled phase 3 clinical trial (S014989). In this trial, 255 patients were randomised to treat capecitabine (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 capecitabine + docetaxel combination arm (p = 0.0126). Median survival was 442 days (capecitabine + docetaxel) vs 352 days (docetaxel alone). The overall objective response rates in the all-randomised population (investigator assessment) were 41.5% (capecitabine + docetaxel) vs 29.7% (docetaxel alone); p = 0.0058. Time to disease progression or death was superior in the capecitabine + docetaxel combination arm (p < 0.0001). The median time to progression was 186 days (capecitabine + docetaxel) vs 128 days (docetaxel alone).

Monotherapy - Breast carcinoma

Two multicentre phase 2 clinical trials were conducted to determine the use of capecitabine 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 238 patients were treated with capecitabine (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.

5.2 Pharmacokinetic properties

Absorption

After oral administration, capecitabine is rapidly and extensively absorbed, followed by extensive conversion to the metabolites, 5'-deoxy-5-fluorocytidine (5'-DFCR) and 5'-DFUR. Administration with food decreases the rate of capecitabine absorption, but only results in a minor effect on the areas under the curve (AUC) of 5'-DFUR, and on the AUC of 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 time to peak plasma concentrations (T_{max} in hours) were 1.50, 2.00, 2.00, 2.00 and 3.34. The AUC_{0-∞} values in ng/ml were 7.75, 7.24, 24.6, 2.03 and 36.3.

Distribution

Protein binding