CAPETERO 150 (Capecitabine Film-Coated Tablet 150mg)
CAPETERO 500 (Capecitabine Film-Coated Tablet 500mg)
2xxxxxx

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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 '6' 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/ m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 7-day rest period.

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

Pre-medication 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/m^2/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/m^2 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 regimen:
In combination with a platinum-based compound the recommended dose of capecitabine for the treatment of advanced gastric cancer is 1000 mg/m^2 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/m^2 twice daily continuously. Epirubicin at a dose of 50 mg/m^2 should be given as a bolus on day 1 every 3 weeks. The platinum based compound (cisplatin at a dose of 60 mg/m^2 (triple regimen) - 80 mg/m^2 (double regimen) or oxaliplatin at a dose of 130 mg/m^2) 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/m^2 or 1000 mg/m^2.

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

Dose level 1250 mg/m^2 (twice daily)					
	Full dose 1250 mg/m^2	Number of tablets per administration (each administration to be given morning and evening)		Reduced dose (75%) 950 mg/m^2	Reduced dose (50%) 625 mg/m^2
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤1.26	1500	-	3	1150	800
1.27 –1.38 1.39 –1.52	1650	1	3	1300	800
1.53 –1.66 1.67 –1.78	1800	2	3	1450	950
1.79 –1.92 1.93 –2.06	2000	-	4	1500	1000
2.07 –2.18 ≥2.19	2150	1	4	1650	1000
	2300	2	4	1800	1150
	2500	-	5	1950	1300
	2650	1	5	2000	1300
	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/m^2

Dose level 1000 mg/m^2 (twice daily)					
	Full dose 1000 mg/m^2	Number of tablets per administration (each administration to be given morning and evening)		Reduced dose (75%) 750 mg/m^2	Reduced dose (50%) 500mg/m^2
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤1.26	1150	1	2	800	600
1.27 –1.38 1.39 –1.52	1300	2	2	1000	600
1.53 –1.66 1.67 –1.78	1450	3	2	1100	750
1.79 –1.92 1.93 –2.06	1600	4	2	1200	800
2.07 –2.18 ≥2.19	1750	5	2	1300	800
	1800	2	3	1400	900
	2000	-	4	1500	1000
	2150	1	4	1600	1050
	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 at a later time.

For those toxicities considered by the treating physician to be unlikely to become serious or life-threatening treatment can be continued at the same dose without reduction or interruption.

Dosage modifications are not recommended for Grade 1 events. Therapy with 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 NCIC grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle (% of starting dose
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to Grade 01	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Discontinue treatment permanently	Not applicable
Grade 3		
1st appearance	Interrupt until resolved to Grade 01	75%
2nd appearance		50%
3rd appearance	Discontinue treatment permanently	Not applicable
Grade 4		
1st appearance	discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to Grade 01	50%
2nd appearance	discontinue permanently	Not applicable

*According to the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG) Common Toxicity Criteria (version 1) or the Common Terminology Criteria for Adverse Events (CTCAE) of the Cancer Therapy Evaluation Program, US National Cancer Institute, version 3.0. For hand-foot syndrome and hyperbilirubinemia.
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

	Recommended Dose Modifications	
	Capecitabine dose changes within a treatment cycle	
Toxicity grade[1]	**Grade 1**	
	100% of starting dose (no interruption)	X: 100% of starting dose T: 100% (75 mg/m^2)
Toxicity grade[1]	**Grade 2**	
1st appearance	Interrupt until resolved (grade 0 – 1)	X: 100% of starting dose T: 100% (75 mg/m^2)
2nd appearance of same toxicity	Interrupt until resolved (grade 0 – 1)	X: 75% of starting dose T: Reduce to 55 mg/m^2
3rd appearance of same toxicity	Interrupt until resolved (grade 0 – 1)	X: 50% of starting dose **T: Discontinue permanently**
4th appearance of same toxicity	**Discontinue permanently**	
Toxicity grade	**Grade 3**	
	If grade 3 haematologicalsee section on haematological toxicity, otherwise:	
1st appearance	Interrupt until resolved (grade 0– 1)	X: 75% of starting dose T: Reduce to 55 mg/m^2
2nd appearance	Interrupt until resolved (grade 0– 1)	X: 50% of starting dose **T: Discontinue permanently**
3rd appearance	**Discontinue permanently**	
Toxicity grade[1]	**Grade 4**	
	If G4 haematological see section on haematological toxicity, otherwise:	
1st appearance	Discontinue permanently or (if physician deems it to be in the best of interest of the patient) interrupt until resolved (grade 0 1)	X: Reduce to 50% **T: Discontinue permanently**
2nd appearance	**Discontinue permanently**	

*National 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.

Hematology: Treatment should only be re-administered when the neutrophil count is ≥ 1.5 x 10^9/l (Grade 0-1). Patients with neutropenia < 0.5 x 10^9/l (Grade 4) for more than 1 week, or febrile (> 38°C) neutropenia, should have the docetaxel dosage reduced from 75 mg/m^2 to 55 mg/m^2. If Grade 4 neutropenia or febrile neutropenia occurs at 55 mg/m^2 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 re 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/m^2. 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 re-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 rehydrated 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

Dose level 950 mg/m^2 twice daily		Number of tablets administered in themorning		Number of tablets administered in the evening	
Body surface area (m^2)	Dose per administration (mg)	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	1500	-	3	-	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	-	4	-	4
≥2.19	2150	1	4	1	4

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

Dose level 625 mg/m^2 twice daily		Number of tablets administered in themorning		Number of tablets administered in the evening	
Body surface area (m^2)	Dose per administration (mg)	150 mg	500 mg	150 mg	500 mg
≤1.38	800	2	1	2	1
1.39 – 1.52	950	3	1	3	1
1.53 – 1.66	1000	-	2	-	2
1.67 – 1.78	1000	-	2	-	2
1.79 – 1.92	1150	1	2	1	2
1.93 –2.06	1300	2	2	2	2
2.07 – 2.18	1300	2	2	2	2
≥2.19	1450	3	2	3	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 60 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/m^2 twice daily) is recommended.

In combination with irinocetan: for patients 65 years of age or more, a starting dose reduction of Capecitabine to 800 mg/ m^2 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/ m^2 is recommended. In patients with mild renal impairment (creatinine clearance 51 - 80 mL/min), no adjustment in starting dose is recommended.

Careful monitoring and prompt treatment interruption is recommended if the patient develops a Grade 2, 3, or 4 ADRs with subsequent dose adjustment as outlined in Table 3 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 given fluid and electrolyte replacement. Standard anti-diarrhea treatments (e.g. loperamide) should be initiated, as medically appropriate, as early as possible. Dose reduction should be applied as necessary.

Dehydration: Dehydration should be prevented or corrected at the onset. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated.
Dehydration may cause acute renal failure, especially in patients with pre-existing compromised renal function or when capecitabine is given concomitantly with known nephrotoxic agents. Fatal outcome of renal failure has been reported in these situations.

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 ADR as necessary.

Dihydropyrimidine dehydrogenase (DPD) deficiency: Rarely, unexpected, severe toxicity (e.g. stomatitis, diarrhea, mucosal inflammation, neutropenia and neurotoxicity) associated with 5-FU has been attributed to a deficiency of DPD activity, an enzyme involved in fluorouracil degradation.

Patients with certain homozygous or certain compound heterozygous mutations in the *DPYD* gene locus that cause complete or near complete absence of DPD activity, are at the highest risk for severe, life-threatening, or fatal adverse reactions caused by fluorouracil. These patients should not be treated with Capecitabine. No dose has been proven safe for patients with complete absence of DPD activity.

Patients with certain heterozygous *DPYD* variants (eg. DPYD*2A variant) that may cause partial DPD deficiency have been shown to have increased risk of severe toxicity when treated with capecitabine. For patients with partial DPD deficiency where the benefits of Capecitabine are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution, initially with a substantial dose reduction and frequent subsequent monitoring and dose adjustment according to toxicity.

Testing for DPD deficiency should be considered based on the local availability and current guidelines.

In patients with unrecognised DPD deficiency treated with capecitabine as well as patients who test negative for specific *DPYD* variations, life-threatening toxicities manifesting as acute 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.

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

Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN). Capecitabine should be permanently discontinued in patients who experience a severe skin reaction possibly attributable to Capecitabine treatment.

Capecitabine can induce hand-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) which is a cutaneous toxicity. Persistent or severe hand-foot syndrome (grade 2 and above) can eventually lead to loss of fingerprints, which could impact patient identification. For patients receiving Capecitabine monotherapy in the metastatic setting, the median time to onset of 79 days, range from 11 to 360 days), with a severity range of Grades 1 to 3.

Grade 1 hand-foot syndrome is defined by numbness, dysesthesia/paresthesia, tingling, or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 is defined as painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patient's activities of daily living. Grade 3 is defined as moist desquamation, ulceration, blistering or severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. If Grade 2 or 3 hand-foot syndrome occurs, administration of Capecitabine should be interrupted until the event resolves or decreases in intensity to Grade 1. Following Grade 3 hand-foot syndrome, subsequent doses of Capecitabine should be decreased. When Capecitabine and cisplatin are used in combination, use of Vitamin B6 (pyridoxine) is not advised for the symptomatic or secondary prophylactic treatment of hand-foot syndrome, because of published reports that it may decrease the efficacy of cisplatin. There is some evidence that dexpanthenol is effective for hand-foot syndrome prophylaxis in patients treated with Capecitabine.

Capecitabine can induce hyperbilirubinemia. Administration of Capecitabine should be interrupted if treatment-related elevations in bilirubin of > 3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2.5 x ULN occur. Treatment may be resumed when bilirubin decreases to ≤3.0 x ULN or hepatic aminotransferases decrease to ≤2.5 x ULN.

Care should be exercised when Capecitabine is co-administered with drugs, which are metabolized by cytochrome P450 2C9 such as for example warfarin or phenytoin. Patients receiving concomitant Capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely and the anticoagulant dose adjusted accordingly. Patients taking phenytoin concomitantly with Capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

Use in special populations
Pediatric Use
The safety and efficacy of capecitabine in pediatric patients below the age of 18 have not been established.

Geriatric Use
Among patients with colorectal cancer aged 60-79 years receiving capecitabine monotherapy in the metastatic setting, the incidence of gastrointestinal toxicity was similar to that in the overall population. In patients aged 80 years or older, a larger percentage experienced reversible Grade 3 or 4 gastrointestinal ADRs, such as diarrhea, nausea and vomiting. When capecitabine was used in combination with other agents geriatric patients (≥ 65 years) experienced more Grade 3 and Grade 4 ADRs and ADRs that led to discontinuation than younger patients. An analysis of safety data in patients equal to or greater than 60 years of age treated with capecitabine plus docetaxel combination therapy showed an increase in the incidence of treatment-related Grade 3 and 4 ADRs, treatment-related serious ADRs and early withdrawals from treatment due to ADRs compared to patients less than 60 years of age.

Renal Impairment
Physicians should exercise caution when capecitabine is administered to patients with impaired renal function. As seen with 5-FU the incidence of treatment-related Grade 3 or 4 ADRs was higher in patients with moderate renal impairment (creatinine clearance 30-50 mL/min).

Hepatic Impairment
Patients with hepatic impairment should be carefully monitored when capecitabine is administered. The effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of capecitabine is not known.

4.5 Interaction with other medicinal products and other forms of interaction
Coumarin anticoagulants
Altered coagulation parameters and/or bleeding have been reported in patients taking Capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating Capecitabine therapy and, in a few cases, within one month after stopping Capecitabine. In a clinical interaction 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 value. These results suggest an interaction, probably due to an inhibition of the cytochrome P450 2C9 isoenzyme system by capecitabine. Patients taking coumarin-derivative anticoagulants concomitantly with Capecitabine should be monitored regularly for alterations in their coagulation parameters (PT or INR) and the anti-coagulant dose adjusted accordingly.

Cytochrome P-450 2C9 substrates
No formal drug-drug interaction studies with capecitabine and other drugs known to be metabolized by the cytochrome P450 2C9 isoenzyme have been conducted. Care should be exercised when Capecitabine is co-administered with these drugs.

Phenytoin
Increased phenytoin plasma concentrations have been reported during concomitant use of Capecitabine with phenytoin. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme system by capecitabine. Patients taking phenytoin concomitantly with Capecitabine should be regularly monitored for increased phenytoin plasma concentrations.

Drug-food interaction
In all clinical trials, patients were instructed to take Capecitabine within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that Capecitabine be administered with food.

Antacid
The effect of an aluminium hydroxide and magnesium hydroxide-containing antacid on the pharmacokinetics of Capecitabine was investigated in cancer patients. There was a small increase in plasma concentrations of capecitabine and one metabolite (5'DFCR); there was no effect on the 3 major metabolites (5'DFUR, 5-FU and FBAL).

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

Sorivudine and analogues:
A clinically significant drug-drug interaction between sorivudine and 5-FU, resulting from the inhibition of dihydropyrimidine dehydrogenase by sorivudine, has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal. Therefore, Capecitabine should not be administered concomitantly with sorivudine or its chemically related analogues, such as brivudine. There must be at least a 4-week waiting period between the end of treatment with sorivudine or its chemically related analogues such as brivudine and start of Capecitabine therapy.

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

Bevacizumab
There was no clinically significant effect of bevacizumab on the pharmacokinetic parameters of capecitabine or its metabolites.

4.6 Female and Males of Reproductive Potential
Fertility
Based on evidence from animal studies, CAPETERO 500 may impair fertility in females and males of reproductive potential.

Females
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine. An effective method of contraception should be used during treatment and for 6 months after the last dose of capecitabine. If the patient becomes pregnant while receiving capecitabine, the potential hazard to the foetus must be explained.

Males
Based on genetic toxicity findings, male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of capecitabine.

Pregnancy
There are no studies in pregnant women using capecitabine; however, based on the pharmacological and toxicological properties of capecitabine, it can be assumed that capecitabine may cause fetal harm if administered to pregnant women. In reproductive toxicity studies in animals, capecitabine administration caused embryolethality and teratogenicity. These findings are expected effects of fluoropyrimidine derivatives. Capecitabine should be considered a potential human teratogen. Capecitabine should not be used during pregnancy. If capecitabine is used during pregnancy or if the patient becomes pregnant while receiving this drug, the patient must be apprised of the potential hazard to the fetus.

Lactation
It is not known whether capecitabine is excreted in human breast milk. No studies have been conducted to assess the impact of capecitabine on milk production or its presence in human breast milk. In lactating mice, considerable amounts of capecitabine and its metabolites were found in milk. As the potential for harm to the nursing infant is unknown, breastfeeding should be discontinued while receiving treatment with capecitabine and for 2 weeks after the final dose.

Pediatric Use
The safety and efficacy of CAPETERO in pediatric patients below the age of 18 have not been established.

Geriatric Use
Among patients with colorectal cancer aged 60-79 years receiving CAPETERO monotherapy in the metastatic setting, the incidence of gastrointestinal toxicity was similar to that in the overall population. In patients aged 80 years or older, a larger percentage experienced reversible Grade 3 or 4 gastrointestinal ADRs, such as diarrhea, nausea and vomiting. When CAPETERO was used in combination with other agents geriatric patients (≥ 65 years) experienced more Grade 3 and Grade 4 ADRs and ADRs that led to discontinuation than younger patients. An analysis of safety data in patients equal to or greater than 60 years of age treated with CAPETERO plus docetaxel combination therapy showed an increase in the incidence of treatment-related Grade 3 and 4 ADRs, treatment-related serious ADRs and early withdrawals from treatment due to ADRs compared to patients less than 60 years of age.

Renal Impairment
Physicians should exercise caution when CAPETERO is administered to patients with impaired renal function. As seen with 5-FU the incidence of treatment-related Grade 3 or 4 ADRs was higher in patients with moderate renal impairment (creatinine clearance 30-50 mL/min).

Hepatic Impairment
Patients with hepatic impairment should be carefully monitored when CAPETERO is administered. The effect of hepatic impairment not due to liver metastases or severe hepatic impairment on the disposition of CAPETERO is not known.

4.7 Effect on ability to drive and use machines
Capecitabine has moderate influence on the ability to drive and use machines. Patients should be advised to use caution when driving or using machines if they experience ADRs such as dizziness, fatigue, and or nausea during treatment with capecitabine.

4.8 Adverse effects
Adverse Drug Reactions (ADRs) considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine have been obtained from clinical studies conducted with Capecitabine monotherapy (in adjuvant therapy of colon cancer, in metastatic colorectal cancer and metastatic breast cancer), and clinical studies conducted with Capecitabine in combination with different chemotherapy regimens for multiple indications. ADRs are added to the appropriate category in the tables below according to the highest incidence from the pooled analysis of seven clinical trials. Within each frequency grouping ADRs are listed in descending order of seriousness. Frequencies are defined as very common ≥ 1/10, common ≥ 5/100 to < 1/10 and uncommon ≥ 1/1000 to < 1/100.

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

Table 7 Summary of related ADRs reported in ≥5% of patients treated with capecitabine monotherapy

Body System ADR	Very Common (10%)	Common (5% to < 10%)
Metabolism and nutrition disorders	Anorexia	Dehydration (G3/4: 3%) , Appetite decreased (G3/4: < 1%)
Nervous system disorders	-	Parasthesia Dysgeusia (G3/4: <1%) Headache (G3/4: <1%), Dizziness (excl. vertigo) (G3/4: <1%),
Eye disorders	-	Lacrimation increased, Conjunctivitis (G3/4: <1%)
Gastrointestinal disorders	Diarrhoea (G3/4: 13%), Vomiting (G3/4: 4%), Nausea (G3/4: 4%), Stomatitis (all)* (G3/4: 4%), Abdominal pain (G3/4: 3%)	Constipation (G3/4: <1%), , Abdominal pain upper (G3/4: <1%), Dyspepsia (G3/4: <1%)
Hepatobiliary disorders	-	Hyperbilirubinemia (G3/4:1%)
Skin and subcutaneous tissue disorders	Palmarplantar erythrodysaesthesia syndrome** (G3/4: 17%), Dermatitis (G3/4: <1%)	Rash, Alopecia, Erythema (G3/4:1%), Dry skin (G3/4: <1%) , Pigmentation disorder, Nail disorder
General disorders and administration site conditions	Fatigue (G3/4: 3%), Asthenia (G3/4: <1%)	Pyrexia (G3/4: <1%), Weakness (G3/4: <1%), Asthenia (G3/4: <1%)

* stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration

** Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints.

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

The following ADRs represent known toxicities with fluoropyrimidine therapy and were reported to be at least remotely related to Capecitabine in less than 5% of patients in seven completed clinical trials (N = 949):

- Gastrointestinal disorder: dry mouth, flatulence, ADRs related to inflammation/ulceration of mucous membranes such as esophagitis, gastritis, duodenitis, colitis, gastrointestinal hemorrhage.
- Cardiac disorders: edema lower limb, cardiac chest pain including angina, cardiomyopathy, myocardial ischemia/infarction, cardiac failure, sudden death, tachycardia, atrial arrhythmias including atrial fibrillation, and ventricular extrasystoles.
- Nervous system disorders: taste disturbance, insomnia, confusion, encephalopathy, and cerebellar signs such as ataxia, dysarthria, impaired balance, abnormal coordination.
- Infections and infestations: ADRs related to bone marrow depression, immune system compromise, and/or disruption of mucous membranes such as local and fatal systemic infections (including bacterial, viral, fungal etiologies) and sepsis.
- Blood and lymphatic system disorders: anemia, bone marrow depression/ pancytopenia.
- Skin and subcutaneous tissue disorders: pruritus, localized exfoliation, skin hyperpigmentation, nail disorders, photosensitivity reactions, radiation recall syndrome
- General disorders and administration site conditions: pain in limb, chest pain (non-cardiac). - Eye: eye irritation.
- Respiratory: dyspnoea, cough - Musculoskeletal: back pain, myalgia, arthralgia
- Psychiatric disorders: depression
- Hepatic failure and cholestatic hepatitis have been reported during clinical trials and post-marketing exposure. A causal relationship with Capecitabine treatment has not been established.

CAPETERO in combination therapy
Table 8 lists ADRs associated with the use of Capecitabine in combination therapy with different chemotherapy regimens in multiple indications and occurred in addition to those seen with monotherapy and/or at a higher frequency grouping. The safety profile was similar across all indications and combination regimens. These reactions occurred in ≥5% of patients treated with Capecitabine in combination with other chemotherapies. Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin), or with bevacizumab (e.g. hypertension); however, an exacerbation by Capecitabine therapy cannot be excluded.

Table 8: Very common and common ADRs for CAPETERO in combination with different chemotherapies in addition to those seen for CAPETERO monotherapy

Body System	Very Common	Common
Infections and infestations	-	Infection+ Oral candidiasis
Blood and lymphatic system disorders	Neutropenia+, Leukopenia+, Febrile Neutropenia+, , Thrombocytopenia+, Anaemia+	
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia, Weight Decreased
Psychiatric disorders	-	Insomnia
Nervous system disorders	Neuropathy Peripheral, Peripheral sensory neuropathy, Paraesthesia, Dysgeusia, Dysaesthesia, Headache	Hypoaesthesia
Eye disorders	Lacrimation increased	
Vascular Disorders	Thrombosis/embolism, Hypertension, Lower limb oedema	
Respiratory, thoracic and mediastinal disorders	Dysaesthesia pharynx Sore throat	Epistaxis, Dysphonia, Rhinorrhoea, Dyspnoea

Dimensions 270 x 700mm
Color: Black

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 63/4 ADRs only.
Hypersensitivity reactions (2%) and cardiac ischaemia/infarction (3%) have been reported commonly for Capecitabine in combination with other chemotherapy but in 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 6: Laboratory abnormalities*; CAPETERO monotherapy in adjuvant colon cancer and in metastatic breast and colorectal cancer.

Parameter	Capecitabine 1250 mg/m2 twice daily interrmint
	Patients with Grade 3/4 abnormally (%)
Increased ALAT (SGPT)	1.6
Increased ASAT (SGOT)	1.1
Increased alkaline phosphate	3.5
Increased calcium	1.1
Decreased calcium	2.3
Decreased granulocytes	0.3
Decreased haemoglobin	3.1
Decreased lymphocytes	44.4
Decreased neutrophiles	3.6
Decreased neutrophiles/ granulocytes	2.4
Decreased platelets	2.0
Decreased potassium	0.3
Increased serum creatinine	0.5
Decreased sodium	0.4
Increased bilirubin	20.0
Hyperglycemia	4.4

*Laboratories abnormalities were graded according to the categories of the NCIC CTC Grading system
The following adverse effects have been identified during post-marketing experience with CAPETERO 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 (≥ 1/1,000 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	Hypertriglyceridemia	*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 CAPETERO tablets, the following ADRs have been reported: eye irritation, eye swelling, skin rash, headache, paresthesia, diarrhea, 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: L01BC06

Mechanism of action
Capecitabine is a fluoropyrimidine carbamate derivative, which was designed as an orally administered, tumour-activated and tumour-selective cytotoxic agent. Capecitabine is non-cytotoxic *in vitro*. However, in vivo, it is sequentially converted to the cytotoxic moiety, 5-fluorouracil (5-FU), which is further metabolised.
Formation of 5-FU is catalysed preferentially at the tumour site by the tumour-associated angiogenic factor thymidine phosphorylase (dThdPase), thereby minimising the exposure of healthy tissues to systemic 5-FU.
The sequential enzymatic biotransformation of capecitabine to 5-FU leads to higher concentrations of 5-FU within tumour tissues. Following oral administration of capecitabine to patients with colorectal cancer (N = 8), the ratio of 5-FU concentration in colorectal tumours vs adjacent tissues was 3.2 (ranged from 0.9 to 8.0). The ratio of 5-FU concentration in tumour vs plasma was 21.4 (ranged from 3.9 to 59.9) whereas the ratio in healthy tissues to plasma was 8.9 (ranged from 3.0 to 25.8). Thymidine phosphorylase activity was 4 times greater in primary colorectal tumour than in adjacent normal tissue.
Several human tumours, such as breast, gastric, colorectal, cervical and ovarian cancers, have a higher level of thymidine phosphorylase (capable of converting 5' OFUR (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 N5-10-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 adjuvant colon cancer
Data from one 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 (XACT 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/LV in disease-free survival (DFS) (p < 0.0001, non-inferiority margin 1.2). In the all-randomized population, tests for difference of capecitabine vs 5-FU/LV in DFS and overall survival (OS) showed hazard ratios of 0.88 (95% CI 0.77-1.01; p = 0.068) and 0.86 (0.74-1.01; p = 0.060), respectively. The median follow up at the time of the analysis was 6.9 years.
Combination therapy in adjuvant colon cancer
Capecitabine in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer has been studied in a multicenter, randomized, controlled phase 3 clinical trial in patients with stage III Dukes' C) colon cancer (NO16968 study). In this trial, 944 patients were randomized to 3-week cycles for 24 weeks with capecitabine (1000 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 randomized to bolus 5-FU and leucovorin. In the primary analysis for DFS, in the ITT population, XELOX was shown to be significantly superior to 5-FU/LV (HR = 0.80, (95% CI 0.69, 0.92); p = 0.0045). The 3-year DFS rate was 71% for XELOX versus 67% for 5-FU/LV. The analysis for the secondary endpoint of relapse free survival (RFS) supports these results with a HR of 0.78 (95% CI 0.67, 0.92; p = 0.0024) for XELOX vs. 5-FU/LV. XELOX showed a trend towards superior OS with a HR of 0.87 (95% CI 0.72, 1.05; p = 0.1486) which translates into a 13% reduction in risk of death. The 5-year OS rate was 78% for XELOX versus 74% for 5-FU/LV. The efficacy data provided is based on a median observation time of 59 months for OS and 57 months for DFS.
At 7 years median follow up, XELOX maintained a statistically significant superior disease-free survival HR = 0.80 (95% CI: 0.69, 0.93; p = 0.0038), and relapse-free survival HR = 0.78 (95% CI: 0.67, 0.91; p = 0.0015). The DFS rate at 7 years was 73% in the XELOX arm and 67% in the 5-FU/LV arm. The additional two years of follow up after the primary analysis show an increase in the difference between survival rates from 3% to 6%.
Monotherapy with capecitabine in metastatic colorectal cancer
Data from two identically-designed, multicenter, randomized, controlled, phase 3 clinical trials support the use of capecitabine for first-line treatment of metastatic colorectal cancer (SO14695; SO14798). In these trials, 603 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 604 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 multicenter, randomized, controlled phase 3 clinical study (NO16966) 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 randomized to two different treatment groups, including XELOX or FOLFOX-4, and a subsequent 2x2 factorial part with four different treatment groups, including XELOX + placebo (P), FOLFOX-4 +P, XELOX + BV, and FOLFOX-4 + BV. The treatment regimens are summarized in Table 8 below.

Table 8: Treatment regimens in study NO16966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + Avastin	Oxaliplatin	85 mg/m² intravenous 2 hr	Oxaliplatin on Day 1, every 2 weeks
	Leucovorin	200 mg/m² intravenous 2 hr	leucovorin on Days 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m² intravenous bolus, followed by 600 mg/m² 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/m² intravenous 2 hr	Oxaliplatin on Day 1, every 3weeks Capecitabine oral twice daily for 2 weeks (followed by 1 week off treatment)
	Capecitabine	1000 mg/m² oral bid	
	Placebo or Avastin	7.5 mg/kg intravenous 3090 mins	Day 1, prior to XELOX, every 3 weeks

5 fluorouracil: Intravenous bolusinjection 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 (97.5% CI 0.84, 1.22). The median follow up at the time of the primary analyses in the intent-to-treat population was 1.5 years; data from analyses following an additional 1 year of follow up are also included in the Table 9 below.

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

PRIMARY ANALYSIS			
	XELOX/XELOX + P/ XELOX + BV (EPP*: N = 967; ITT**: N= 1017)	FOLFOX-4/FOLFOX-4 + P/ FOLFOX-4 + BV (EPP*: N = 937; ITT**: N= 1017)	
Population	**Median Time to Event (Days)**		**HR (97.5% CI)**
Parameter: Progressionfree Survival			
EPP	241	259	1.05 (0.94; 1.18)
ITT	244	259	1.04 (0.93; 1.16)
Parameter: OverallSurvival			
EPP	577	549	0.97 (0.84; 1.14)
ITT	581	553	0.96 (0.83; 1.12)
ADDITIONAL 1 YEAR OF FOLLOW UP			
Population	**Median Time to Event (Days)**		**HR (97.5% CI)**
Parameter: Progressionfree Survival			
EPP	242	259	1.02 (0.92; 1.14)
ITT	244	259	1.01 (0.91;1.12)
Parameter: Overall Survival			
EPP	600	594	1.00 (0.88; 1.13)
ITT	602	596	0.99 (0.88; 1.12)

*EPP = eligible-patient population; **ITT = intent-to-treat population
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, leucovorin, and irinotecan (FOLFIRI).
Capecitabine (at a starting dose of 800 mg/m² for 2 weeks every 3 weeks) in combination with irinotecan and bevacizumab was studied for the first-line treatment of patients with metastatic colorectal cancer, in a multicentre, randomized, controlled phase II study (AIO KRK 0604) 128 patients were randomized to treatment with capecitabine combined with irinotecan (XELIRI) and bevacizumab: capecitabine (800 mg/m² twice daily for two weeks followed by a 7-day rest period), irinotecan (200 mg/m² as a 30 to 90 minute infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 to minute infusion on day 1 every 3 weeks); a total of 127 patients were randomized to treatment with capecitabine combined with oxaliplatin (XELOX) plus bevacizumab: capecitabine (1000 mg/m² twice daily for two weeks followed by a 7-day rest period), oxaliplatin (130 mg/m² as a 2 hour infusion on day 1 every 3 weeks), and bevacizumab (7.5 mg/kg as a 30 to 90 minute infusion on day 1 every 3 weeks). The mean duration of follow-up for the study population was 26.6 months. Progression-free survival at 6 months in the intent-to treat population was 64% (XELIRI plus bevacizumab) versus 76% (XELOX plus bevacizumab). Overall response rate (complete response plus partial response) was 50% (XELIRI plus bevacizumab) versus 53% (XELOX plus bevacizumab). The median overall survival was 25.5 months (XELIRI plus bevacizumab) and 24.4 months (XELOX plus bevacizumab).
Combination therapy – Second line treatment of colorectal cancer
Study NO16967 was a multicenter, randomized, controlled phase III trial that studied the use of capecitabine in combination with oxaliplatin for the second-line treatment of metastatic colorectal cancer. In this trial, 627 patients with metastatic colorectal carcinoma who have received prior treatment with irinotecan in combination with a fluoropyrimidine regimen as first-line therapy were randomized to treatment with XELOX or FOLFOX-4. For the dosing schedule of XELOX and FOLFOX-4 (without addition of placebo or bevacizumab), refer to Table 8. XELOX was demonstrated to be non-inferior to FOLFOX-4 in terms of progression-free survival in the per-protocol population and intent-to-treat population.The results indicate that XELOX is equivalent to FOLFOX-4 in terms of OS. The median follow up at the time of the primary analyses in the intent-to-treat population was 2.1 years; data from analyses following an additional 6 months of follow up are also included in the Table 10 below.

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

PRIMARY ANALYSIS			
XELOX (PPP*: N = 251; ITT**: N = 313)		FOLFOX-4 (EPP*: N = 252; ITT**: N = 314)	
Population	**Median Time to Event (Days)**		**HR (97.5% CI)**
Parameter: Progressionfree 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	363	382	1.03 (0.87; 1.23)
ADDITIONAL 6 MONTHS OF FOLLOW UP			
Population	**Median Time to Event (Days)**		**HR (95% CI)**
Parameter: Progressionfree 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	363	382	1.02 (0.86; 1.21)

*PPP = per-protocol population; **ITT = intent-to-treat population
A pooled analysis of the efficacy data from first-line (study NO16966; initial 2-arm part) and second line treatment (study NO16967) further support the non-inferiority results of XELOX versus FOLFOX-4 as obtained in the individual studies: progression-free survival in the per-protocol population (hazard ratio 1.00 (95% CI: 0.88; 1.14)) with a median progression-free survival of 193 days (XELOX; 508 patients) versus 204 days (FOLFOX-4; 500 patients). The results indicate that XELOX is equivalent to FOLFOX-4 in terms of OS (hazard ratio 1.01(95% CI: 0.87; 1.17) with a median OS of 468 days (XELOX) versus 478 days (FOLFOX-4).
Combination therapy – Oesophagogastric cancer
A multicenter, randomized, 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, 160 patients were randomized to treat 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 randomized to treatment with 5-FU (800 mg/m² per day, continous 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 ML17033)

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

* Unadjusted treatment effect in Cox proportional model.
Data from a randomised multicentre, phase 3 study (REAL 2) comparing capecitabine to 5-FU and oxaliplatin to cisplatin in patients with advanced oesophagogastric cancer supports the use of capecitabine for the first-line treatment of advanced oesophagogastric cancer. In this trial, 1002 patients were randomised in a 2x2 factorial design to one of the following 4 arms:

– ECF: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m² as a two hour infusion on day 1 every 3 weeks) and 5-FU (200 mg/m² daily given by continuous infusion via a central line),
– ECX: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), cisplatin (60 mg/m² as a two hour infusion on day 1 every 3 weeks), and 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 three weeks), and 5-FU (200 mg/m² daily given by continous infusion via a central line).
– EOX: epirubicin (50 mg/m² as a bolus on day 1 every 3 weeks), oxaliplatin (130 mg/m² given as a 2 hour infusion on day 1 every three weeks), and 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 - 0.99) and for oxaliplatin vs cisplatin-based regimens (hazard ratio 0.92; 95% CI 0.80 - 1.1). The median overall survival was 10.0 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, randomized, multicenter (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 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 taken place.
A total of 1035 patients were randomized 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 266 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 = 0.56 (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 0.66 (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 SO14695, SO14796, 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 multicenter, randomized, controlled phase 3 clinical trial (SO14990). In this trial, 255 patients were randomized 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 randomized 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 = 0.0128). Median survival was 442 days (capecitabine + docetaxel) vs 352 days (docetaxel alone). The overall objective response rates in the all-randomized population (investigator assessment) were 41.6% (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 multicenter 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 236 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 of 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_{∞} values in µghr/ml were 7.75, 7.24, 24.6, 2.03 and 36.3.
Distribution
Protein binding
In vitro human plasma studies have determined that capecitabine, 5'-DFCR, 5'-DFUR and 5-FU are 54%, 10%, 62% and 10% protein bound, mainly to albumin.
Metabolism
Capecitabine is first metabolised by hepatic carboxylesterase to 5'-DFCR, which is then converted to 5'-DFUR by cytidine deaminase, principally located in the liver and tumour tissues.
Formation of 5-FU occurs preferentially at the tumour site by the tumour-associated angiogenic factor dThdPase, thereby minimising the exposure of healthy body tissues to systemic 5-FU.
The plasma AUC of 5-FU is 6 to 22 times lower than that following an intravenous bolus of 5-FU (dose of 600 mg/m²). The metabolites of capecitabine become cytotoxic only after conversion to 5-FU and anabolites of 5-FU.
5-FU is further catabolized to the inactive metabolites dihydro-5-fluorouracil (FUH_2). 5-fluoro-ureidopropionic acid (FUPA) and α-fluoro-β-alanine (FBAL) via dihydropyrimidine dehydrogenase (DPD), which is rate limiting.
Elimination
The elimination half-lives ($t_{1/2}$ in hours) of capecitabine, 5'-DFCR, 5'-DFUR, 5-FU and FBAL were 0.85, 1.11, 0.66, 0.76 and 3.23 respectively. The pharmacokinetics of capecitabine have been evaluated over a dose range of 502 - 3514 mg/m²/day. The parameters of capecitabine, 5'-DFCR and 5'-DFUR measured on days 1 and 14 were similar. The AUC of 5-FU was 30-35% higher on day 14, but did not increase subsequently (day 22). At therapeutic doses, the pharmacokinetics of capecitabine and its metabolites were dose proportional, except for 5-FU.
After oral administration capecitabine metabolites are primarily recovered in the urine. Most (95.5%) of administered capecitabine dose is recovered in urine. Faecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL, which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.
Combination therapy
Phase I studies evaluating the effect of capecitabine on the pharmacokinetics of either docetaxel or paclitaxel and vice versa showed no effect by capecitabine on the pharmacokinetics of docetaxel or paclitaxel; IC_{50} and AUC and no effect by docetaxel or paclitaxel on the pharmacokinetics of 5' DFUR (the most important metabolite of capecitabine).
Pharmacokinetics in special populations
A population pharmacokinetic analysis was carried out after capecitabine treatment of 505 patients with colorectal cancer dosed at 1250 mg/m² twice daily. Gender, presence or absence of liver metastasis at baseline, Karnofsky Performance Status, total bilirubin, serum albumin, ASAT and ALAT had no statistically significant effect on the pharmacokinetics of 5'DFUR, 5-FU and FBAL.
Hepatic impairment due to liver metastases
No clinically significant effect on the bioactivation and pharmacokinetics of capecitabine was observed in cancer patients with mildly to moderately impaired liver function due to liver metastases.
No formal pharmacokinetic study has been conducted and no population pharmacokinetic data was collected in patients with severe hepatic impairment.
Renal impairment
Based on a pharmacokinetic study in cancer patients with mild to severe renal impairment, there is no evidence for an effect of creatinine clearance on the pharmacokinetics of intact drug and 5-FU. Creatinine clearance was found to influence the systemic exposure to 5'-DFUR (35% increase in AUC when creatinine clearance decreases by 50%) and to FBAL (114% increase in AUC when creatinine clearance decreases by 50%). FBAL is a metabolite without antiproliferative activity; 5'-DFUR is the direct precursor of 5-FU.
Geriatric Population
Based on the population pharmacokinetic analysis, which included patients with a wide range of ages (27 to 86 years) and included 234 (46%) patients greater or equal to 65, age has no influence on the pharmacokinetics of 5' DFUR and 5-FU. The AUC of FBAL increased with age (20% increase in age results in a 15% increase in the AUC of FBAL). This increase is likely due to a change in renal function.
Race
Based on population pharmacokinetic analysis of 455 white patients (90.1%), 22 black patients (4.4%) and 28 patients of other race or ethnicity (5.5%), the pharmacokinetics of capecitabine in black patients were not different compared to white patients.

6. PHARMACEUTICALS PARTICULARS

6.1 List of excipients
Anhydrous lactose
Cellulose Microcrystalline
Hypromellose
Croscarmellose Sodium
Magnesium Stearate
Opadry Pink 03A04598

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium- free'.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Storage condition
Store below 30°C and protect from moisture.

6.5 Packaging available
CAPETERO 150 & 500: 3 x 10's Alu Alu Blister Pack

7. NAME AND ADDRESS OF MANUFACTURER

HETERO LABS LIMITED, Unit 5,
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8. PRODUCT REGISTRATION HOLDER

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9. DATE OF REVISION

04th November 2025