1.4.1 Prescribing information (Summary of products characteristics)

1. Name of the Finished pharmaceutical product

INN Name: Capecitabine Tablets USP 500 mg

Trade Name: CAPETERO 500

Strength: 500 mg

Pharmaceutical form: Tablet

2. Qualitative and quantitative composition

Each film coated tablet contains 500 mg of Capecitabine USP.

For Excipients kindly refer to 6.1 list of excipients

3. Pharmaceutical form

Dosage form: Film coated Tablet

Description: Peach colored, 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

Colorectal Cancer

CAPECITABINE TABLETS USP 500 MG is indicated as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred. CAPECITABINE TABLETS USP 500 MG was non-inferior to 5-fluorouracil and leucovorin (5-FU/LV) for disease-free survival (DFS). Physicians should consider results of combination chemotherapy trials, which have shown improvement in DFS and OS, when prescribing single-agent CAPECITABINE TABLETS USP 500 MG in the adjuvant treatment of Dukes' C colon cancer.

CAPECITABINE TABLETS USP 500 MG is indicated as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred.

Combination chemotherapy has shown a survival benefit compared to 5-FU/LV alone. A survival benefit over 5-FU/LV has not been demonstrated with CAPECITABINE TABLETS USP 500 MG monotherapy. Use of CAPECITABINE TABLETS USP 500 MG instead of 5-FU/LV in combinations has not been adequately studied to assure safety or preservation of the survival advantage.

Breast Cancer

CAPECITABINE TABLETS USP 500 MG in combination with docetaxel is indicated for the treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy.

CAPECITABINE TABLETS USP 500 MG monotherapy is also indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated (e.g., patients who have received cumulative doses of 400 mg/m2 of doxorubicin or doxorubicin equivalents). Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen.

4.2 Posology and method of administration

CAPECITABINE TABLETS USP 500 MG tablets should be swallowed whole with water within 30 minutes after a meal. CAPECITABINE TABLETS USP 500 MG dose is calculated according to body surface area.

Standard Starting Dose

Monotherapy (Metastatic Colorectal Cancer, Adjuvant Colorectal Cancer, Metastatic Breast Cancer)

The recommended dose of CAPECITABINE TABLETS USP 500 MG is 1250 mg/m2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles (see Table 1).

Adjuvant treatment in patients with Dukes' C colon cancer is recommended for a total of 6 months [ie, CAPECITABINE TABLETS USP 500 MG 1250 mg/m2 orally twice daily for 2 weeks followed by a 1-week rest period, given as 3-week cycles for a total of 8 cycles (24 weeks)].

Table 1 CAPECITABINE TABLETS USP 500 MG Dose Calculation According to Body Surface Area

Dose Level 1250 mg/m2 Twice a Day			**t Each**
Surface Area (m2)	**Total Daily Dose (mg)**	**150 mg**	**500 mg**
≤ 1.25	3000	0	3
1.26-1.37	3300	1	3
1.38-1.51	3600	2	3
1.52-1.65	4000	0	4
1.66-1.77	4300	1	4
1.78-1.91	4600	2	4
1.92-2.05	5000	0	5
2.06-2.17	5300	1	5
≥ 2.18	5600	2	5

In Combination With Docetaxel (Metastatic Breast Cancer)

In combination with docetaxel, the recommended dose of CAPECITABINE TABLETS USP 500 MG is 1250 mg/m2 twice daily for 2 weeks followed by a 1-week rest period, combined with docetaxel at 75 mg/m2 as a 1-hour intravenous infusion every 3 weeks. Pre-medication, according to the docetaxel labeling, should be started prior to docetaxel administration for patients receiving the CAPECITABINE TABLETS USP 500 MG plus docetaxel combination. Table 1 displays the total daily dose of CAPECITABINE TABLETS USP 500 MG by body surface area and the number of tablets to be taken at each dose.

Dose Management Guidelines

General

CAPECITABINE TABLETS USP 500 MG dosage may need to be individualized to optimize patient management. Patients should be carefully monitored for toxicity and doses of CAPECITABINE TABLETS USP 500 MG should be modified as necessary to accommodate individual patient tolerance to treatment .Toxicity due to CAPECITABINE TABLETS USP 500 MG administration may be managed by symptomatic treatment, dose interruptions and adjustment of CAPECITABINE TABLETS USP 500 MG dose. Once the dose has been reduced, it should not be increased at a later time. Doses of CAPECITABINE TABLETS USP 500 MG omitted for toxicity are not replaced or restored; instead the patient should resume the planned treatment cycles.

The dose of phenytoin and the dose of coumarin-derivative anticoagulants may need to be reduced when either drug is administered concomitantly with CAPECITABINE TABLETS USP 500 MG.

Monotherapy (Metastatic Colorectal Cancer, Adjuvant Colorectal Cancer, Metastatic Breast Cancer)

CAPECITABINE TABLETS USP 500 MG dose modification scheme as described below (see Table 2) is recommended for the management of adverse reactions.

Table 2 Recommended Dose Modifications of CAPECITABINE TABLETS USP 500 MG

Toxicity NCIC Grades	**During a Course of Therapy**	**Dose Adjustment for Next Treatment (% of starting dose)**
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%

-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	-
Grade 3		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	-
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 0-1	50%

In Combination With Docetaxel (Metastatic Breast Cancer)

Dose modifications of CAPECITABINE TABLETS USP 500 MG for toxicity should be made according to Table 2 above for CAPECITABINE TABLETS USP 500 MG. At the beginning of a treatment cycle, if a treatment delay is indicated for either CAPECITABINE TABLETS USP 500 MG or docetaxel, then administration of both agents should be delayed until the requirements for restarting both drugs are met.

The dose reduction schedule for docetaxel when used in combination with CAPECITABINE TABLETS USP 500 MG for the treatment of metastatic breast cancer is shown in Table 3.

Table 3 Docetaxel Dose Reduction Schedule in Combination with CAPECITABINE TABLETS USP 500 MG

Toxicity NCIC Grades	**Grade 2**	**Grade 3**

1st appearance	Delay treatment until resolved to grade 0-1; Resume treatment with original dose of 75 mg/m2 docetaxel	Delay treatment until resolved to grade 0-1; Resume treatment at 55 mg/m2 of docetaxel.
2nd appearance	Delay treatment until resolved to grade 0-1; Resume treatment at 55 mg/m2 of docetaxel.	Discontinue treatment with docetaxel
3rd appearance	Discontinue treatment with docetaxel	-

Adjustment of Starting Dose in Special Populations

Renal Impairment

No adjustment to the starting dose of CAPECITABINE TABLETS USP 500 MG is recommended in patients with mild renal impairment (creatinine clearance = 51 to 80 mL/min [Cockroft and Gault, as shown below]). In patients with moderate renal impairment (baseline creatinine clearance = 30 to 50 mL/min), a dose reduction to 75% of the CAPECITABINE TABLETS USP 500 MG starting dose when used as monotherapy or in combination with docetaxel (from 1250 mg/m2 to 950 mg/m2 twice daily) is recommended Subsequent dose adjustment is recommended as outlined in Table 2 and Table 3 (depending on the regimen) if a patient develops a grade 2 to 4 adverse event The starting dose adjustment recommendations for patients with moderate renal impairment apply to both CAPECITABINE TABLETS USP 500 MG monotherapy and CAPECITABINE TABLETS USP 500 MG in combination use with docetaxel.

Cockroft and Gault Equation:	
	(140 - age [yrs]) (body wt [kg])
Creatinine clearance for males =	————————————————

	(72) (serum creatinine [mg/dL])
Creatinine clearance for females = 0.85 × male value	

Geriatrics

Physicians should exercise caution in monitoring the effects of CAPECITABINE TABLETS USP 500 MG in the elderly. Insufficient data are available to provide a dosage recommendation.

4.3 Contraindications

Dihydropyrimidine Dehydrogenase (DPD) Deficiency

CAPECITABINE TABLETS USP 500 MG is contraindicated in patients with known dihydropyrimidine dehydrogenase (DPD) deficiency.

Severe Renal Impairment

CAPECITABINE TABLETS USP 500 MG is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).

Hypersensitivity

CAPECITABINE TABLETS USP 500 MG is contraindicated in patients with known hypersensitivity to capecitabine or to any of its components. CAPECITABINE TABLETS USP 500 MG is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil.

4.4 Special warnings and precautions for use

General

Patients receiving therapy with CAPECITABINE TABLETS USP 500 MG should be monitored by a physician experienced in the use of cancer chemotherapeutic agents. Most adverse reactions

are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced.

Diarrhea

CAPECITABINE TABLETS USP 500 MG can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. In 875 patients with either metastatic breast or colorectal cancer who received CAPECITABINE TABLETS USP 500 MG monotherapy, the median time to first occurrence of grade 2 to 4 diarrhea was 34 days (range from 1 to 369 days). The median duration of grade 3 to 4 diarrhea was 5 days. National Cancer Institute of Canada (NCIC) grade 2 diarrhea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an increase of ≥10 stools/day or grossly bloody diarrhea or the need for parenteral support. If grade 2, 3 or 4 diarrhea occurs, administration of CAPECITABINE TABLETS USP 500 MG should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1. Following a reoccurrence of grade 2 diarrhea or occurrence of any grade 3 or 4 diarrhea, subsequent doses of CAPECITABINE TABLETS USP 500 MG should be decreased.Standard antidiarrheal treatments (eg, loperamide) are recommended.

Necrotizing enterocolitis (typhlitis) has been reported.

Coagulopathy

Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly.

Cardiotoxicity

The cardiotoxicity observed with CAPECITABINE TABLETS USP 500 MG includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden

death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

Dihydropyrimidine Dehydrogenase Deficiency

Rarely, unexpected, severe toxicity (eg, stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. A link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-fluorouracil therefore cannot be excluded.

Renal Insufficiency

Patients with moderate renal impairment at baseline require dose reduction .Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse reactions. Prompt interruption of therapy with subsequent dose adjustments is recommended if a patient develops a grade 2 to 4 adverse event as outlined in Table 2.

Pregnancy

CAPECITABINE TABLETS USP 500 MG may cause fetal harm when given to a pregnant woman. Capecitabine caused embryolethality and teratogenicity in mice and embryolethality in monkeys when administered during organogenesis. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving CAPECITABINE TABLETS USP 500 MG, the patient should be apprised of the potential hazard to the fetus.

Hand-and-Foot Syndrome

Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity. Median time to onset was 79 days (range from 11 to 360 days) with a severity range of grades 1 to 3 for patients receiving CAPECITABINE TABLETS USP 500 MG monotherapy in the metastatic setting. Grade 1 is characterized by any of the following: numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. Grade 2 hand-and-foot syndrome

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 hand-and-foot syndrome 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-and-foot syndrome occurs, administration of CAPECITABINE TABLETS USP 500 MG should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of CAPECITABINE TABLETS USP 500 MG should be decreased.

Hyperbilirubinemia

In 875 patients with either metastatic breast or colorectal cancer who received at least one dose of CAPECITABINE TABLETS USP 500 MG 1250 mg/m2 twice daily as monotherapy for 2 weeks followed by a 1-week rest period, grade 3 (1.5-3 × ULN) hyperbilirubinemia occurred in 15.2% (n=133) of patients and grade 4 (>3 × ULN) hyperbilirubinemia occurred in 3.9% (n=34) of patients. Of 566 patients who had hepatic metastases at baseline and 309 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 22.8% and 12.3%, respectively. Of the 167 patients with grade 3 or 4 hyperbilirubinemia, 18.6% (n=31) also had postbaseline elevations (grades 1 to 4, without elevations at baseline) in alkaline phosphatase and 27.5% (n=46) had postbaseline elevations in transaminases at any time (not necessarily concurrent). The majority of these patients, 64.5% (n=20) and 71.7% (n=33), had liver metastases at baseline. In addition, 57.5% (n=96) and 35.3% (n=59) of the 167 patients had elevations (grades 1 to 4) at both prebaseline and postbaseline in alkaline phosphatase or transaminases, respectively. Only 7.8% (n=13) and 3.0% (n=5) had grade 3 or 4 elevations in alkaline phosphatase or transaminases.

In the 596 patients treated with CAPECITABINE TABLETS USP 500 MG as first-line therapy for metastatic colorectal cancer, the incidence of grade 3 or 4 hyperbilirubinemia was similar to the overall clinical trial safety database of CAPECITABINE TABLETS USP 500 MG monotherapy. The median time to onset for grade 3 or 4 hyperbilirubinemia in the colorectal cancer population was 64 days and median total bilirubin increased from 8 µm/L at baseline to 13 µm/L during treatment with CAPECITABINE TABLETS USP 500 MG. Of the 136

colorectal cancer patients with grade 3 or 4 hyperbilirubinemia, 49 patients had grade 3 or 4 hyperbilirubinemia as their last measured value, of which 46 had liver metastases at baseline.

In 251 patients with metastatic breast cancer who received a combination of CAPECITABINE TABLETS USP 500 MG and docetaxel, grade 3 (1.5 to 3 × ULN) hyperbilirubinemia occurred in 7% (n=17) and grade 4 (>3 × ULN) hyperbilirubinemia occurred in 2% (n=5).

If drug-related grade 3 to 4 elevations in bilirubin occur, administration of CAPECITABINE TABLETS USP 500 MG should be immediately interrupted until the hyperbilirubinemia decreases to ≤3.0 X ULN.

Hematologic

In 875 patients with either metastatic breast or colorectal cancer who received a dose of 1250 mg/m2 administered twice daily as monotherapy for 2 weeks followed by a 1-week rest period, 3.2%, 1.7%, and 2.4% of patients had grade 3 or 4 neutropenia, thrombocytopenia or decreases in hemoglobin, respectively. In 251 patients with metastatic breast cancer who received a dose of CAPECITABINE TABLETS USP 500 MG in combination with docetaxel, 68% had grade 3 or 4 neutropenia, 2.8% had grade 3 or 4 thrombocytopenia, and 9.6% had grade 3 or 4 anemia.

Patients with baseline neutrophil counts of <1.5 × 109/L and/or thrombocyte counts of <100 × 109/L should not be treated with CAPECITABINE TABLETS USP 500 MG. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 hematologic toxicity, treatment with CAPECITABINE TABLETS USP 500 MG should be interrupted.

Geriatric Patients

Patients ≥80 years old may experience a greater incidence of grade 3 or 4 adverse reactions. In 875 patients with either metastatic breast or colorectal cancer who received CAPECITABINE TABLETS USP 500 MG monotherapy, 62% of the 21 patients ≥80 years of age treated with CAPECITABINE TABLETS USP 500 MG experienced a treatment-related grade 3 or 4 adverse event: diarrhea in 6 (28.6%), nausea in 3 (14.3%), hand-and-foot syndrome in 3 (14.3%), and vomiting in 2 (9.5%) patients. Among the 10 patients 70 years of age and greater (no patients

were >80 years of age) treated with CAPECITABINE TABLETS USP 500 MG in combination with docetaxel, 30% (3 out of 10) of patients experienced grade 3 or 4 diarrhea and stomatitis, and 40% (4 out of 10) experienced grade 3 hand-and-foot syndrome.

Among the 67 patients ≥60 years of age receiving CAPECITABINE TABLETS USP 500 MG in combination with docetaxel, the incidence of grade 3 or 4 treatment-related adverse reactions, treatment-related serious adverse reactions, withdrawals due to adverse reactions, treatment discontinuations due to adverse reactions and treatment discontinuations within the first two treatment cycles was higher than in the <60 years of age patient group.

In 995 patients receiving CAPECITABINE TABLETS USP 500 MG as adjuvant therapy for Dukes' C colon cancer after resection of the primary tumor, 41% of the 398 patients ≥65 years of age treated with CAPECITABINE TABLETS USP 500 MG experienced a treatment-related grade 3 or 4 adverse event: hand-and-foot syndrome in 75 (18.8%), diarrhea in 52 (13.1%), stomatitis in 12 (3.0%), neutropenia/granulocytopenia in 11 (2.8%), vomiting in 6 (1.5%), and nausea in 5 (1.3%) patients. In patients ≥65 years of age (all randomized population; capecitabine 188 patients, 5-FU/LV 208 patients) treated for Dukes' C colon cancer after resection of the primary tumor, the hazard ratios for disease-free survival and overall survival for CAPECITABINE TABLETS USP 500 MG compared to 5-FU/LV were 1.01 (95% C.I. 0.80 – 1.27) and 1.04 (95% C.I. 0.79 – 1.37), respectively.

Hepatic Insufficiency

Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when CAPECITABINE TABLETS USP 500 MG is administered. The effect of severe hepatic dysfunction on the disposition of CAPECITABINE TABLETS USP 500 MG is not known

Combination With Other Drugs

Use of CAPECITABINE TABLETS USP 500 MG in combination with irinotecan has not been adequately studied.

4.5 Interaction with other medicinal products and other forms of interaction

Drug-Drug Interactions

Anticoagulants

Altered coagulation parameters and/or bleeding have been reported in patients taking CAPECITABINE TABLETS USP 500 MG concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon . These events occurred within several days and up to several months after initiating CAPECITABINE TABLETS USP 500 MG therapy and, in a few cases, within 1 month after stopping CAPECITABINE TABLETS USP 500 MG. These events occurred in patients with and without liver metastases. In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin . The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Phenytoin

The level of phenytoin should be carefully monitored in patients taking CAPECITABINE TABLETS USP 500 MG and phenytoin dose may need to be reduced . Postmarketing reports indicate that some patients receiving CAPECITABINE TABLETS USP 500 MG and phenytoin had toxicity associated with elevated phenytoin levels. 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 by capecitabine and/or its metabolites.

Leucovorin

The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil.

CYP2C9 substrates

Other than warfarin, no formal drug-drug interaction studies between CAPECITABINE TABLETS USP 500 MG and other CYP2C9 substrates have been conducted. Care should be exercised when CAPECITABINE TABLETS USP 500 MG is coadministered with CYP2C9 substrates.

Drug-Food Interaction

Food was shown to reduce both the rate and extent of absorption of capecitabine . In all clinical trials, patients were instructed to administer CAPECITABINE TABLETS USP 500 MG within 30 minutes after a meal. It is recommended that CAPECITABINE TABLETS USP 500 MG be administered with food.

4.6 Pregnancy and lactation

CAPECITABINE TABLETS USP 500 MG can cause fetal harm when administered to a pregnant woman. Capecitabine at doses of 198 mg/kg/day during organogenesis caused malformations and embryo death in mice. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.2 times the corresponding values in patients administered the recommended daily dose. Malformations in mice included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilation of cerebral ventricles. At doses of 90 mg/kg/day, capecitabine given to pregnant monkeys during organogenesis caused fetal death. This dose produced 5'-DFUR AUC values about 0.6 times the corresponding values in patients administered the recommended daily dose.

There are no adequate and well controlled studies of CAPECITABINE TABLETS USP 500 MG in pregnant women. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving CAPECITABINE TABLETS USP 500 MG, the patient should be apprised of the potential hazard to the fetus. Women should be advised to avoid becoming pregnant while receiving treatment with CAPECITABINE TABLETS USP 500 MG.

Nursing Mothers

Lactating mice given a single oral dose of capecitabine excreted significant amounts of capecitabine metabolites into the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from capecitabine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Fertility, pregnancy and lactation

Please refer to 4.6.

4.8 Effects on ability to drive and use machines

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

4.9 Undesirable Effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Colon Cancer

Table 5 shows the adverse reactions occurring in ≥5% of patients from one phase 3 trial in patients with Dukes' C colon cancer who received at least one dose of study medication and had at least one safety assessment. A total of 995 patients were treated with 1250 mg/m2 twice a day of CAPECITABINE TABLETS USP 500 MG administered for 2 weeks followed by a 1-week rest period, and 974 patients were administered 5-FU and leucovorin (20 mg/m2 leucovorin IV followed by 425 mg/m2 IV bolus 5-FU on days 1-5 every 28 days). The median duration of treatment was 164 days for capecitabine-treated patients and 145 days for 5-FU/LV-treated patients. A total of 112 (11%) and 73 (7%) capecitabine and 5-FU/LV-treated patients, respectively, discontinued treatment because of adverse reactions. A total of 18 deaths due to all

causes occurred either on study or within 28 days of receiving study drug: 8 (0.8%) patients randomized to CAPECITABINE TABLETS USP 500 MG and 10 (1.0%) randomized to 5-FU/LV.

Table 6 shows grade 3/4 laboratory abnormalities occurring in ≥1% of patients from one phase 3 trial in patients with Dukes' C colon cancer who received at least one dose of study medication and had at least one safety assessment.

Table 5 Percent Incidence of Adverse Reactions Reported in ≥5% of Patients Treated With CAPECITABINE TABLETS USP 500 MG or 5-FU/LV for Colon Cancer in the Adjuvant Setting (Safety Population)

	Adjuvant Treatment for Colon Cancer (N=1969)			
	CAPECITABINE TABLETS USP 500 MG (N=995)		**5-FU/LV (N=974)**	
Body System/ Adverse Event	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Gastrointestinal Disorders				
Diarrhea	47	12	65	14
Nausea	34	2	47	2
Stomatitis	22	2	60	14
Vomiting	15	2	21	2
Abdominal Pain	14	3	16	2
Constipation	9	-	11	<1
Upper Abdominal Pain	7	<1	7	<1
Dyspepsia	6	<1	5	-
Skin and Subcutaneous				

Tissue Disorders				
Hand-and-Foot Syndrome	60	17	9	<1
Alopecia	6	-	22	<1
Rash	7	-	8	-
Erythema	6	1	5	<1
General Disorders and Administration Site Conditions				
Fatigue	16	<1	16	1
Pyrexia	7	<1	9	<1
Asthenia	10	<1	10	1
Lethargy	10	<1	9	<1
Nervous System Disorders				
Dizziness	6	<1	6	-
Headache	5	<1	6	<1
Dysgeusia	6	-	9	-
Metabolism and Nutrition Disorders				
Anorexia	9	<1	11	<1
Eye Disorders				
Conjunctivitis	5	<1	6	<1
Blood and Lymphatic System Disorders				

Neutropenia	2	<1	8	5
Respiratory Thoracic and Mediastinal Disorders				
Epistaxis	2	-	5	-

Table 6 Percent Incidence of Grade 3/4 Laboratory Abnormalities Reported in ≥1% of Patients Receiving CAPECITABINE TABLETS USP 500 MG Monotherapy for Adjuvant Treatment of Colon Cancer (Safety Population)

Adverse Event	**CAPECITABINE TABLETS USP 500 MG (n=995) Grade 3/4 %**	**IV 5-FU/LV (n=974) Grade 3/4 %**
Increased ALAT (SGPT)	1.6	0.6
Increased calcium	1.1	0.7
Decreased calcium	2.3	2.2
Decreased hemoglobin	1.0	1.2
Decreased lymphocytes	13.0	13.0
Decreased neutrophils	2.2	26.2
Decreased neutrophils/granulocytes	2.4	26.4
Decreased platelets	1.0	0.7
Increased bilirubin	20	6.3

Metastatic Colorectal Cancer

Monotherapy

Table 7 shows the adverse reactions occurring in ≥5% of patients from pooling the two phase 3 trials in first line metastatic colorectal cancer. A total of 596 patients with metastatic colorectal cancer were treated with 1250 mg/m2 twice a day of CAPECITABINE TABLETS USP 500 MG administered for 2 weeks followed by a 1-week rest period, and 593 patients were administered 5-FU and leucovorin in the Mayo regimen (20 mg/m2 leucovorin IV followed by 425 mg/m2 IV bolus 5-FU, on days 1-5, every 28 days). In the pooled colorectal database the median duration of treatment was 139 days for capecitabine-treated patients and 140 days for 5-FU/LV-treated patients. A total of 78 (13%) and 63 (11%) capecitabine and 5-FU/LV-treated patients, respectively, discontinued treatment because of adverse reactions/intercurrent illness. A total of 82 deaths due to all causes occurred either on study or within 28 days of receiving study drug: 50 (8.4%) patients randomized to CAPECITABINE TABLETS USP 500 MG and 32 (5.4%) randomized to 5-FU/LV.

Table 7 Pooled Phase 3 Colorectal Trials: Percent Incidence of Adverse Reactions in ≥5% of Patients

Adverse Event	**CAPECITABINE TABLETS USP 500 MG (n=596)**			**5-FU/LV (n=593)**		
	Total %	**Grade 3 %**	**Grade 4 %**	**Total %**	**Grade 3 %**	**Grade 4 %**
Number of Patients With > One Adverse Event	96	52	9	94	45	9
Body System/Adverse Event						
GI						
Diarrhea	55	13	2	61	10	2
Nausea	43	4	–	51	3	<1
Vomiting	27	4	<1	30	4	<1

Stomatitis	25	2	<1	62	14	1
Abdominal Pain	35	9	<1	31	5	–
Gastrointestinal Motility Disorder	10	<1	–	7	<1	–
Constipation	14	1	<1	17	1	–
Oral Discomfort	10	–	–	10	–	–
Upper GI Inflammatory Disorders	8	<1	–	10	1	–
Gastrointestinal Hemorrhage	6	1	<1	3	1	–
Ileus	6	4	1	5	2	1
Skin and Subcutaneous						
Hand-and-Foot Syndrome	54	17	NA	6	1	NA
Dermatitis	27	1	–	26	1	–
Skin Discoloration	7	<1	–	5	–	–
Alopecia	6	–	–	21	<1	–
General						
Fatigue/Weakness	42	4	–	46	4	–
Pyrexia	18	1	–	21	2	–
Edema	15	1	–	9	1	–
Pain	12	1	–	10	1	–
Chest Pain	6	1	–	6	1	<1
Neurological						
Peripheral Sensory Neuropathy	10	–	–	4	–	–
Headache	10	1	–	7	–	–
Dizziness	8	<1	–	8	<1	–

Insomnia	7	–	–	7	–	–
Taste Disturbance	6	1	–	11	<1	1
Metabolism						
Appetite Decreased	26	3	<1	31	2	<1
Dehydration	7	2	<1	8	3	1
Eye						
Eye Irritation	13	–	–	10	<1	–
Vision Abnormal	5	–	–	2	–	–
Respiratory						
Dyspnea	14	1	–	10	<1	1
Cough	7	<1	1	8	–	–
Pharyngeal Disorder	5	–	–	5	–	–
Epistaxis	3	<1	–	6	–	–
Sore Throat	2	–	–	6	–	–
Musculoskeletal						
Back Pain	10	2	–	9	<1	–
Arthralgia	8	1	–	6	1	–
Vascular						
Venous Thrombosis	8	3	<1	6	2	–
Psychiatric						
Mood Alteration	5	–	–	6	<1	–
Depression	5	–	–	4	<1	–
Infections						
Viral	5	<1	–	5	<1	–
Blood and Lymphatic						
Anemia	80	2	<1	79	1	<1
Neutropenia	13	1	2	46	8	13

Hepatobiliary						
Hyperbilirubinemia	48	18	5	17	3	3

– Not observed

NA = Not Applicable

Breast Cancer

In Combination with Docetaxel

The following data are shown for the combination study with CAPECITABINE TABLETS USP 500 MG and docetaxel in patients with metastatic breast cancer in Table 8 and Table 9 . In the CAPECITABINE TABLETS USP 500 MG and docetaxel combination arm the treatment was CAPECITABINE TABLETS USP 500 MG administered orally 1250 mg/m2 twice daily as intermittent therapy (2 weeks of treatment followed by 1 week without treatment) for at least 6 weeks and docetaxel administered as a 1-hour intravenous infusion at a dose of 75 mg/m2 on the first day of each 3-week cycle for at least 6 weeks. In the monotherapy arm docetaxel was administered as a 1-hour intravenous infusion at a dose of 100 mg/m2 on the first day of each 3-week cycle for at least 6 weeks. The mean duration of treatment was 129 days in the combination arm and 98 days in the monotherapy arm. A total of 66 patients (26%) in the combination arm and 49 (19%) in the monotherapy arm withdrew from the study because of adverse reactions. The percentage of patients requiring dose reductions due to adverse reactions was 65% in the combination arm and 36% in the monotherapy arm. The percentage of patients requiring treatment interruptions due to adverse reactions in the combination arm was 79%. Treatment interruptions were part of the dose modification scheme for the combination therapy arm but not for the docetaxel monotherapy-treated patients.

Table 8 Percent Incidence of Adverse Events Considered Related or Unrelated to Treatment in ≥5% of Patients Participating in the CAPECITABINE TABLETS USP 500 MG and Docetaxel Combination vs Docetaxel Monotherapy Study

Adverse Event	**CAPECITABINE TABLETS**	**Docetaxel**

	USP 500 MG 1250 mg/m2/bid With Docetaxel 75 mg/m2/3 weeks (n=251)			**100 mg/m2/3 weeks (n=255)**		
	Total %	**Grade 3 %**	**Grade 4 %**	**Total %**	**Grade 3 %**	**Grade 4 %**
Number of Patients With at Least One Adverse Event	99	76.5	29.1	97	57.6	31.8
Body System/Adverse Event						
GI						
Diarrhea	67	14	<1	48	5	<1
Stomatitis	67	17	<1	43	5	–
Nausea	45	7	–	36	2	–
Vomiting	35	4	1	24	2	–
Constipation	20	2	–	18	–	–
Abdominal Pain	30	<3	<1	24	2	–
Dyspepsia	14	–	–	8	1	–
Dry Mouth	6	<1	–	5	–	–
Skin and Subcutaneous						
Hand-and-Foot Syndrome	63	24	NA	8	1	NA
Alopecia	41	6	–	42	7	–
Nail Disorder	14	2	–	15	–	–
Dermatitis	8	–	–	11	1	–
Rash Erythematous	9	<1	–	5	–	–
Nail Discoloration	6	–	–	4	<1	–
Onycholysis	5	1	–	5	1	–
Pruritus	4	–	–	5	–	–

General						
Pyrexia	28	2	–	34	2	–
Asthenia	26	4	<1	25	6	–
Fatigue	22	4	–	27	6	–
Weakness	16	2	–	11	2	–
Pain in Limb	13	<1	–	13	2	–
Lethargy	7	–	–	6	2	–
Pain	7	<1	–	5	1	–
Chest Pain (non-cardiac)	4	<1	–	6	2	–
Influenza-like Illness	5	–	–	5	–	–
Neurological						
Taste Disturbance	16	<1	–	14	<1	–
Headache	15	3	–	15	2	–
Paresthesia	12	<1	–	16	1	–
Dizziness	12	–	–	8	<1	–
Insomnia	8	–	–	10	<1	–
Peripheral Neuropathy	6	–	–	10	1	–
Hypoaesthesia	4	<1	–	8	<1	–
Metabolism						
Anorexia	13	1	–	11	<1	–
Appetite Decreased	10	–	–	5	–	–
Weight Decreased	7	–	–	5	–	–
Dehydration	10	2	–	7	<1	<1
Eye						
Lacrimation Increased	12	–	–	7	<1	–
Conjunctivitis	5	–	–	4	–	–
Eye Irritation	5	–	–	1	–	–
Musculoskeletal						
Arthralgia	15	2	–	24	3	–

Myalgia	15	2	–	25	2	–
Back Pain	12	<1	–	11	3	–
Bone Pain	8	<1	–	10	2	–
Cardiac						
Edema	33	<2	–	34	<3	1
Blood						
Neutropenic Fever	16	3	13	21	5	16
Respiratory						
Dyspnea	14	2	<1	16	2	–
Cough	13	1	–	22	<1	–
Sore Throat	12	2	–	11	<1	–
Epistaxis	7	<1	–	6	–	–
Rhinorrhea	5	–	–	3	–	–
Pleural Effusion	2	1	–	7	4	–
Infection						
Oral Candidiasis	7	<1	–	8	<1	–
Urinary Tract Infection	6	<1	–	4	–	–
Upper Respiratory Tract	4	–	–	5	1	–
Vascular						
Flushing	5	–	–	5	–	–
Lymphoedema	3	<1	–	5	1	–
Psychiatric						
Depression	5	–	–	5	1	–

– Not observed

NA = Not Applicable

Table 9 Percent of Patients With Laboratory Abnormalities Participating in the

CAPECITABINE TABLETS USP 500 MG and Docetaxel Combination vs Docetaxel Monotherapy Study

Adverse Event	**CAPECITABINE TABLETS USP 500 MG 1250 mg/m2/bid With Docetaxel 75 mg/m2/3 weeks (n=251)**				**weeks**
Body System/Adverse Event	**Total %**	**Grade 3 %**	**Grade 4 %**	**Total %**	**Grade 3 %**
Hematologic					
Leukopenia	91	37	24	88	42
Neutropenia/Granulocytopenia	86	20	49	87	10
Thrombocytopenia	41	2	1	23	1
Anemia	80	7	3	83	5
Lymphocytopenia	99	48	41	98	44
Hepatobiliary					

Monotherapy

The following data are shown for the study in stage IV breast cancer patients who received a dose of 1250 mg/m2 administered twice daily for 2 weeks followed by a 1-week rest period. The mean duration of treatment was 114 days. A total of 13 out of 162 patients (8%) discontinued treatment because of adverse reactions/intercurrent illness.

Table 10 Percent Incidence of Adverse Reactions Considered Remotely, Possibly or Probably Related to Treatment in ≥5% of Patients Participating in the Single Arm Trial in Stage IV Breast Cancer

Adverse Event	**Phase 2 Trial in Stage IV Breast Cancer (n=162)**		
Body System/Adverse Event	**Total %**	**Grade 3 %**	**Grade 4 %**
GI			
Diarrhea	57	12	3
Nausea	53	4	–
Vomiting	37	4	–
Stomatitis	24	7	–
Abdominal Pain	20	4	–
Constipation	15	1	–
Dyspepsia	8	–	–
Skin and Subcutaneous			
Hand-and-Foot Syndrome	57	11	NA
Dermatitis	37	1	–
Nail Disorder	7	–	–
General			
Fatigue	41	8	–
Pyrexia	12	1	–
Pain in Limb	6	1	–
Neurological			
Paresthesia	21	1	–
Headache	9	1	–
Dizziness	8	–	–
Insomnia	8	–	–
Metabolism			
Anorexia	23	3	–

Dehydration	7	4	1
Eye			
Eye Irritation	15	–	–
Musculoskeletal			
Myalgia	9	–	–
Cardiac			
Edema	9	1	–
Blood			
Neutropenia	26	2	2
Thrombocytopenia	24	3	1
Anemia	72	3	1
Lymphopenia	94	44	15
Hepatobiliary			
Hyperbilirubinemia	22	9	2

– Not observed			
NA = Not Applicable			
GI			
Diarrhea	57	12	3
Nausea	53	4	–
Vomiting	37	4	–
Stomatitis	24	7	–
Abdominal Pain	20	4	–
Constipation	15	1	–
Dyspepsia	8	–	–
Skin and Subcutaneous			
Hand-and-Foot Syndrome	57	11	NA
Dermatitis	37	1	–

Nail Disorder	7	–	–
General			
Fatigue	41	8	–
Pyrexia	12	1	–
Pain in Limb	6	1	–
Neurological			
Paresthesia	21	1	–
Headache	9	1	–
Dizziness	8	–	–
Insomnia	8	–	–
Metabolism			
Anorexia	23	3	–
Dehydration	7	4	1
Eye			
Eye Irritation	15	–	–
Musculoskeletal			
Myalgia	9	–	–
Cardiac			
Edema	9	1	–
Blood			
Neutropenia	26	2	2
Thrombocytopenia	24	3	1
Anemia	72	3	1
Lymphopenia	94	44	15
Hepatobiliary			
Hyperbilirubinemia	22	9	2

Clinically Relevant Adverse Events in <5% of Patients

Clinically relevant adverse events reported in <5% of patients treated with CAPECITABINE TABLETS USP 500 MG either as monotherapy or in combination with docetaxol that were

considered at least remotely related to treatment are shown below; occurrences of each grade 3 and 4 adverse event are provided in parentheses.

Monotherapy (Metastatic Colorectal Cancer, Adjuvant Colorectal Cancer, Metastatic Breast Cancer)

Gastrointestinal:	abdominal distension, dysphagia, proctalgia, ascites (0.1%), gastric ulcer (0.1%), ileus (0.3%), toxic dilation of intestine, gastroenteritis (0.1%)
Skin & Subcutan.:	nail disorder (0.1%), sweating increased (0.1%), photosensitivity reaction (0.1%), skin ulceration, pruritus, radiation recall syndrome (0.2%)
General:	chest pain (0.2%), influenza-like illness, hot flushes, pain (0.1%), hoarseness, irritability, difficulty in walking, thirst, chest mass, collapse, fibrosis (0.1%), hemorrhage, edema, sedation
Neurological:	insomnia, ataxia (0.5%), tremor, dysphasia, encephalopathy (0.1%), abnormal coordination, dysarthria, loss of consciousness (0.2%), impaired balance
Metabolism:	increased weight, cachexia (0.4%), hypertriglyceridemia (0.1%), hypokalemia, hypomagnesemia
Eye:	conjunctivitis
Respiratory:	cough (0.1%), epistaxis (0.1%), asthma (0.2%), hemoptysis, respiratory distress (0.1%), dyspnea
Cardiac:	tachycardia (0.1%), bradycardia, atrial fibrillation, ventricular extrasystoles, extrasystoles, myocarditis (0.1%), pericardial effusion
Infections:	laryngitis (1.0%), bronchitis (0.2%), pneumonia (0.2%), bronchopneumonia (0.2%), keratoconjunctivitis, sepsis (0.3%), fungal infections (including candidiasis) (0.2%)
Musculoskeletal:	myalgia, bone pain (0.1%), arthritis (0.1%), muscle weakness
Blood & Lymphatic:	leukopenia (0.2%), coagulation disorder (0.1%), bone marrow

	depression (0.1%), idiopathic thrombocytopenia purpura (1.0%), pancytopenia (0.1%)
Vascular:	hypotension (0.2%), hypertension (0.1%), lymphoedema (0.1%), pulmonary embolism (0.2%), cerebrovascular accident (0.1%)
Psychiatric:	depression, confusion (0.1%)
Renal:	renal impairment (0.6%)
Ear:	vertigo
Hepatobiliary:	hepatic fibrosis (0.1%), hepatitis (0.1%), cholestatic hepatitis (0.1%), abnormal liver function tests
Immune System:	drug hypersensitivity (0.1%)
Postmarketing:	hepatic failure, lacrimal duct stenosis

CAPECITABINE TABLETS USP 500 MG In Combination With Docetaxel (Metastatic Breast Cancer)

Gastrointestinal:	ileus (0.4%), necrotizing enterocolitis (0.4%), esophageal ulcer (0.4%), hemorrhagic diarrhea (0.8%)
Neurological:	ataxia (0.4%), syncope (1.2%), taste loss (0.8%), polyneuropathy (0.4%), migraine (0.4%)
Cardiac:	supraventricular tachycardia (0.4%)
Infection:	neutropenic sepsis (2.4%), sepsis (0.4%), bronchopneumonia (0.4%)
Blood & Lymphatic:	agranulocytosis (0.4%), prothrombin decreased (0.4%)
Vascular:	hypotension (1.2%), venous phlebitis and thrombophlebitis (0.4%), postural hypotension (0.8%)
Renal:	renal failure (0.4%)
Hepatobiliary:	jaundice (0.4%), abnormal liver function tests (0.4%), hepatic failure (0.4%), hepatic coma (0.4%), hepatotoxicity (0.4%)
Immune System:	hypersensitivity (1.2%)

4.10 Overdose

The manifestations of acute overdose would include nausea, vomiting, diarrhea, gastrointestinal irritation and bleeding, and bone marrow depression. Medical management of overdose should include customary supportive medical interventions aimed at correcting the presenting clinical manifestations. Although no clinical experience using dialysis as a treatment for CAPECITABINE TABLETS USP 500 MG overdose has been reported, dialysis may be of benefit in reducing circulating concentrations of 5'-DFUR, a low–molecular-weight metabolite of the parent compound.

Single doses of CAPECITABINE TABLETS USP 500 MG were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg (2.4, 4.8, and 9.6 times the recommended human daily dose on a mg/m2 basis).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: cytostatic (antimetabolite), ATC code: L01BC06

Mechanism of Action

Enzymes convert capecitabine to 5-fluorouracil (5-FU) in vivo. Both normal and tumor cells metabolize 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 2'-deoxyuridylate. 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.

5.2 Pharmacokinetic properties

Following oral administration of 1255 mg/m2 BID to cancer patients, capecitabine reached peak blood levels in about 1.5 hours (Tmax) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of capecitabine with mean Cmax and AUC0-∞ decreased by 60% and 35%, respectively. The Cmax and AUC0-∞ of 5-FU were also reduced by food by 43% and 21%, respectively. Food delayed Tmax of both parent and 5-FU by 1.5 hours.

The pharmacokinetics of CAPECITABINE TABLETS USP 500 MG and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m2/day. Over this range, the pharmacokinetics of CAPECITABINE TABLETS USP 500 MG and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The interpatient variability in the Cmax and AUC of 5-FU was greater than 85%.

Distribution

Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-dependent. Capecitabine was primarily bound to human albumin (approximately 35%). CAPECITABINE TABLETS USP 500 MG has a low potential for pharmacokinetic interactions related to plasma protein binding.

Bioactivation and Metabolism

Capecitabine is extensively metabolized enzymatically to 5-FU. In the liver, a 60 kDa carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-DFUR. The enzyme, thymidine phosphorylase (dThdPase), then hydrolyzes 5'-DFUR to the active drug 5-FU. Many tissues throughout the body express thymidine phosphorylase. Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues. Following oral administration of CAPECITABINE TABLETS USP

500 MG 7 days before surgery in patients with colorectal cancer, the median ratio of 5-FU concentration in colorectal tumors to adjacent tissues was 2.9 (range from 0.9 to 8.0). These ratios have not been evaluated in breast cancer patients or compared to 5-FU infusion.

The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism, to the much less toxic 5-fluoro-5, 6-dihydro-fluorouracil (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro-β-alanine (FBAL) which is cleared in the urine.

In vitro enzymatic studies with human liver microsomes indicated that capecitabine and its metabolites (5'-DFUR, 5'-DFCR, 5-FU, and FBAL) did not inhibit the metabolism of test substrates by cytochrome P450 isoenzymes 1A2, 2A6, 3A4, 2C19, 2D6, and 2E1.

Excretion

Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Fecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug. The elimination half-life of both parent capecitabine and 5-FU was about 0.75 hour.

Effect of Age, Gender, and Race on the Pharmacokinetics of Capecitabine

A population analysis of pooled data from the two large controlled studies in patients with metastatic colorectal cancer (n=505) who were administered CAPECITABINE TABLETS USP 500 MG at 1250 mg/m2 twice a day indicated that gender (202 females and 303 males) and race (455 white/Caucasian patients, 22 black patients, and 28 patients of other race) have no influence on the pharmacokinetics of 5'-DFUR, 5-FU and FBAL. Age has no significant influence on the pharmacokinetics of 5'-DFUR and 5-FU over the range of 27 to 86 years. A 20% increase in age results in a 15% increase in AUC of FBAL.

Following oral administration of 825 mg/m2 capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower Cmax and 24% lower AUC for capecitabine than the Caucasian patients (n=22). Japanese patients had also about 25% lower Cmax and 34% lower AUC for FBAL than the Caucasian patients. The clinical significance of these differences is unknown. No significant differences occurred in the exposure to other metabolites (5'-DFCR, 5'-DFUR, and 5-FU).

Effect of Hepatic Insufficiency

CAPECITABINE TABLETS USP 500 MG has been evaluated in 13 patients with mild to moderate hepatic dysfunction due to liver metastases defined by a composite score including bilirubin, AST/ALT and alkaline phosphatase following a single 1255 mg/m2 dose of CAPECITABINE TABLETS USP 500 MG. Both AUC0-∞ and Cmax of capecitabine increased by 60% in patients with hepatic dysfunction compared to patients with normal hepatic function (n=14). The AUC0-∞ and Cmax of 5-FU were not affected. In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when CAPECITABINE TABLETS USP 500 MG is administered. The effect of severe hepatic dysfunction on CAPECITABINE TABLETS USP 500 MG is not known.

Effect of Renal Insufficiency

Following oral administration of 1250 mg/m2 capecitabine twice a day to cancer patients with varying degrees of renal impairment, patients with moderate (creatinine clearance = 30 to 50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment showed 85% and 258% higher systemic exposure to FBAL on day 1 compared to normal renal function patients (creatinine clearance >80 mL/min). Systemic exposure to 5'-DFUR was 42% and 71% greater in moderately and severely renal impaired patients, respectively, than in normal patients. Systemic exposure to capecitabine was about 25% greater in both moderately and severely renal impaired patients.

Effect of Capecitabine on the Pharmacokinetics of Warfarin

In four patients with cancer, chronic administration of capecitabine (1250 mg/m2 bid) with a single 20 mg dose of warfarin increased the mean AUC of S-warfarin by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in these 4 patients increased by 2.8-fold, and the maximum observed mean INR value was increased by 91%.

Effect of Antacids on the Pharmacokinetics of Capecitabine

When Maalox® (20 mL), an aluminum hydroxide- and magnesium hydroxide-containing antacid, was administered immediately after CAPECITABINE TABLETS USP 500 MG (1250 mg/m2, n=12 cancer patients), AUC and Cmax increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'-DFCR. No effect was observed on the other three major metabolites (5'-DFUR, 5-FU, FBAL) of CAPECITABINE TABLETS USP 500 MG.

Effect of Capecitabine on the Pharmacokinetics of Docetaxel and Vice Versa

A Phase 1 study evaluated the effect of CAPECITABINE TABLETS USP 500 MG on the pharmacokinetics of docetaxel (Taxotere®) and the effect of docetaxel on the pharmacokinetics of CAPECITABINE TABLETS USP 500 MG was conducted in 26 patients with solid tumors. CAPECITABINE TABLETS USP 500 MG was found to have no effect on the pharmacokinetics of docetaxel (Cmax and AUC) and docetaxel has no effect on the pharmacokinetics of capecitabine and the 5-FU precursor 5'-DFUR.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Adequate studies investigating the carcinogenic potential of CAPECITABINE TABLETS USP 500 MG have not been conducted. Capecitabine was not mutagenic in vitro to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). Capecitabine was clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic in vivo to mouse bone marrow (micronucleus test). Fluorouracil causes mutations in bacteria and yeast. Fluorouracil also causes chromosomal abnormalities in the mouse micronucleus test in vivo.

Impairment of Fertility

In studies of fertility and general reproductive performance in female mice, oral capecitabine doses of 760 mg/kg/day (about 2300 mg/m2/day) disturbed estrus and consequently caused a decrease in fertility. In mice that became pregnant, no fetuses survived this dose. The disturbance in estrus was reversible. In males, this dose caused degenerative changes in the testes, including decreases in the number of spermatocytes and spermatids. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.7 times the corresponding values in patients administered the recommended daily dose.

6. Pharmaceutical particulars

6.1 List of excipients

Anhydrous lactose USP-NF (Supertab 21 AN), Croscarmellose sodium USP-NF (Ac-Di-Sol), Hypromellose 2910 5CPS USP (Methocel E5 LV Premium), Purified water IH/USP/Ph.Eur, Microcrystalline cellulose USP-NF (Avicel PH 112), Magnesium stearate USP-NF, Opadry Pink 03A84408 IH.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30° C, protect from moisture.

6.5 Nature and contents of container

HDPE Container pack: 120’s count

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local

requirements.

7. Marketing Authorisation Holder and Manufacturing Site Addresses

Name: **Hetero Labs Limited**

Business Address: 7-2-A2, Hetero Corporate,
Industrial Estates,
Sanath Nagar,
Hyderabad-500 018
Andhra Pradesh.

Country: INDIA

8. Manufacture

(Company) Name : Hetero Labs Limited (Unit-VI)

Address : Sy No. 410 & 411, TSIIC Formulation SEZ, Polepally Village, Jadcherla Mandal, Mahaboobnagar District, Telangana state, India Country India

Telephone : 91-08542-238400

Telefax : 91-08542 238411

E-Mail : contact@heterodrugs.com;

9. Date of revision of the text
