For the use of a Registered Medical Practitioner only

1. GENERIC NAME AND BRAND NAME

Capecitabine Tablets I.P. 500 mg

Capecite® - 500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Capecitabine I.P. ….500 mg

Excipients …….q.s.

Colours: Ferric oxide USP-NF Red & Titanium Dioxide I.P.

3. DOSAGE FORM & STRENGTH

Refer section 1 & 2

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

1. For the treatment of patients with metastatic colorectal cancer.
2. For the treatment of metastatic breast cancer after failure of paclitaxel and anthracycline containing chemotherapy regimen.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Important Administration Instructions

Capecitabine tablets should be swallowed whole with water within 30 minutes after a meal. Capecitabine is a cytotoxic drug. Follow applicable safe handling and a professional trained in specific handling of cytotoxic drugs using appropriate equipment and safety procedures should do disposal procedures. Capecitabine tablets must be cut or crushed, this. Capecitabine dose is calculated according to body surface area.

Standard Starting Dose

Monotherapy (Metastatic Colorectal Cancer, Metastatic Breast Cancer): The recommended dose of Capecitabine is 1250 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles (see Table 1).

Table 1: Capecitabine Dose Calculation According to Body Surface Area

Dose Level 1250 mg/m^2 Twice a Day		**Number of Tablets to be Taken at Each Dose (Morning and Evening)**	
Surface Area (m^2)	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

*Total Daily Dose divided by 2 to allow equal morning and evening doses

Dose Management Guidelines

General Capecitabine dosage may need to be individualized to optimize patient management. Patients should be carefully monitored for toxicity and doses of Capecitabine should be modified as necessary to accommodate individual patient tolerance to treatment. Toxicity due to Capecitabine administration may be managed by symptomatic treatment, dose interruptions and adjustment of Capecitabine dose. Once the dose has been reduced, it should not be increased at a later time. Doses of Capecitabine 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.

Monotherapy (Metastatic Colorectal Cancer, Metastatic Breast Cancer): Capecitabine dose modification scheme as described below is recommended for the management of adverse reactions.

Table 2: Recommended Dose Modifications of Capecitabine

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%

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

Adjustment of Starting Dose in Special Populations

Renal Impairment No adjustment to the starting dose of Capecitabine 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 starting dose when used as monotherapy or in combination with docetaxel (from 1250 mg/m^2 to 950 mg/m^2 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 monotherapy and Capecitabine in combination use with docetaxel.

Cockroft and Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age [yrs]})\ (\text{body wt [kg]})}{(72)\ (\text{serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value.

Geriatrics

Physicians should exercise caution in monitoring the effects of Capecitabine in the elderly. Insufficient data are available to provide a dosage recommendation.

4.3 CONTRAINDICATIONS

- Capecitabine is contraindicated in patients with known hypersensitivity to capecitabine or to any of its components or fluorouracil. Capecitabine is contraindicated in patients who have a known hypersensitivity to 5fluorouracil.
- Capecitabine is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).
- History of severe and unexpected reactions to fluoropyrimidine therapy,
- In patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity
- During pregnancy and lactation,
- In patients with severe leukopenia, neutropenia, or thrombocytopenia,
- In patients with severe hepatic impairment,
- Recent or concomitant treatment with brivudine
- If contraindications exist to any of the medicinal products in the combination regimen, that medicinal product should not be used.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

Diarrhea

Capecitabine 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 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 should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1. Standard antidiarrheal treatments (e.g., loperamide) are recommended.

Necrotizing enterocolitis (typhlitis) has been reported.

Cardiotoxicity

The cardiotoxicity observed with Capecitabine 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

Based on post marketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by Capecitabine (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by Capecitabine.

Withhold or permanently discontinue Capecitabine based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No Capecitabine dose has been proven safe for patients with complete absence of

DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

Dehydration and Renal Failure

Dehydration has been observed and may cause acute renal failure which can be fatal. Patients with pre-existing compromised renal function or who are receiving concomitant Capecitabine with known nephrotoxic agents are at higher risk. Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated. Monitor patients when Capecitabine is administered to prevent and correct dehydration at the onset. If grade 2 (or higher) dehydration occurs, Capecitabine treatment should be immediately interrupted and the dehydration corrected. Treatment should not be restarted until the patient is rehydrated and any precipitating causes have been corrected or controlled. Dose modifications should be applied for the precipitating adverse event as necessary.

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

Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and its mechanism of action, Capecitabine may cause fetal harm when given to a pregnant woman. Limited available data are not sufficient to inform use of Capecitabine in pregnant women. In animal reproduction studies, administration of capecitabine to pregnant animals during the period of organogenesis caused embryolethality and teratogenicity in mice and embryolethality in monkeys at 0.2 and 0.6 times the exposure (AUC) in patients receiving the recommended dose respectively. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Capecitabine.

Mucocutaneous and Dermatologic Toxicity

Severe mucocutaneous reactions, some with fatal outcome, such as Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN) can occur in patients treated with Capecitabine.

Capecitabine should be permanently discontinued in patients who experience a severe mucocutaneous reaction possibly attributable to Capecitabine treatment.

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 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. Persistent or severe hand-and-foot syndrome (grade 2 and above) can eventually lead to loss of fingerprints which could impact patient identification. If grade 2 or 3 hand-and-foot syndrome occurs, administration of Capecitabine 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 should be decreased.

Hyperbilirubinemia

In 875 patients with either metastatic breast or colorectal cancer who received at least one dose of Capecitabine 1250 mg/m^2 twice daily as monotherapy for 2 weeks followed by a 1-week rest period, grade 3 (1.5-3 x ULN) hyperbilirubinemia occurred in 15.2% (n=133) of patients and grade 4 (>3 x 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 post baseline 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 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 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. 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 and docetaxel, grade 3 (1.5 to 3 x ULN) hyperbilirubinemia occurred in 7% (n=17) and grade 4 (>3 x ULN) hyperbilirubinemia occurred in 2% (n=5).

If drug-related grade 3 to 4 elevations in bilirubin occur, administration of Capecitabine 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 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 x 10^9/L and/or thrombocyte counts of <100 x 10^9/L should not be treated with Capecitabine. If unscheduled laboratory assessments during a treatment cycle show grade 3 or 4 hematologic toxicity, treatment with Capecitabine 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 monotherapy, 62% of the 21 patients ≥80 years of age treated with Capecitabine 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 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 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 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 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 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 is administered. The effect of severe hepatic dysfunction on the disposition of Capecitabine is not known.

Combination with Other Drugs

Use of Capecitabine in combination with irinotecan has not been adequately studied.

4.5 DRUG INTERACTIONS

Anticoagulants

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 1 month after stopping Capecitabine. 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 and phenytoin dose may need to be reduced. Postmarketing reports indicate that some patients receiving Capecitabine 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 and other CYP2C9 substrates have been conducted. Care should be exercised when Capecitabine is administered with CYP2C9 substrates.

Allopurinol

Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites, which may decrease Capecitabine efficacy. Avoid the use of allopurinol during treatment with Capecitabine.

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 within 30 minutes after a meal. It is recommended that Capecitabine be administered with food.

4.6 USE IN SPECIAL POPULATIONS (SUCH AS PREGNANT WOMEN, LACTATING WOMEN, PAEDIATRIC PATIENTS, GERIATRIC PATIENTS ETC.)

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with capecitabine.

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

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, it should be assumed that capecitabine may cause foetal 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 is contraindicated during pregnancy.

Breast-feeding

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.

Fertility

There is no data on Capecitabine and impact on fertility. The Capecitabine pivotal studies included females of childbearing potential and males only if they agreed to use an acceptable method of birth control to avoid pregnancy for the duration of the study and for a reasonable period thereafter. In animal studies effects on fertility were observed.

Paediatric Use

The safety and effectiveness of Capecitabine in pediatric patients have not been established. No clinical benefit was demonstrated in two single arm trials in pediatric patients with newly diagnosed brainstem gliomas and high grade gliomas. In both trials, pediatric patients

received an investigational pediatric formulation of capecitabine concomitantly with and following completion of radiation therapy (total dose of 5580 cGy in 180 cGy fractions). The relative bioavailability of the investigational formulation to Capecitabine was similar.

The first trial was conducted in 22 pediatric patients (median age 8 years, range 5-17 years) with newly diagnosed non-disseminated intrinsic diffuse brainstem gliomas and high grade gliomas. In the dose-finding portion of the trial, patients received capecitabine with concomitant radiation therapy at doses ranging from 500 mg/m^2 to 850 mg/m^2 every 12 hours for up to 9 weeks. After a 2 week break, patients received 1250 mg/m^2 capecitabine every 12 hours on Days 1-14 of a 21day cycle for up to 3 cycles. The maximum tolerated dose (MTD) of capecitabine administered concomitantly with radiation therapy was 650 mg/m^2 every 12 hours. The major dose limiting toxicities were palmar-plantar erythrodysesthesia and alanine aminotransferase (ALT) elevation.

The second trial was conducted in 34 additional pediatric patients with newly diagnosed non-disseminated intrinsic diffuse brainstem gliomas (median age 7 years, range 3-16 years) and 10 pediatric patients who received the MTD of capecitabine in the dose-finding trial and met the eligibility criteria for this trial. All patients received 650 mg/m^2 capecitabine every 12 hours with concomitant radiation therapy for up to 9 weeks. After a 2 week break, patients received 1250 mg/m^2 capecitabine every 12 hours on Days 1-14 of a 21-day cycle for up to 3 cycles.

There was no improvement in one-year progression-free survival rate and one-year overall survival rate in pediatric patients with newly diagnosed intrinsic brainstem gliomas who received capecitabine relative to a similar population of pediatric patients who participated in other clinical trials.

The adverse reaction profile of capecitabine was consistent with the known adverse reaction profile in adults, with the exception of laboratory abnormalities which occurred more commonly in pediatric patients. The most frequently reported laboratory abnormalities (per-patient incidence ≥40%) were increased ALT (75%), lymphocytopenia (73%), leukopenia (73%), hypokalemia (68%), thrombocytopenia (57%), hypoalbuminemia (55%), neutropenia (50%), low hematocrit (50%), hypocalcemia (48%), hypophosphatemia (45%) and hyponatremia (45%).

Geriatric Use

Physicians should pay particular attention to monitoring the adverse effects of Capecitabine in the elderly.

Hepatic Insufficiency

Exercise caution when patients with mild to moderate hepatic dysfunction due to liver metastases are treated with Capecitabine. The effect of severe hepatic dysfunction on Capecitabine is not known

Renal Insufficiency

Patients with moderate (creatinine clearance = 30 to 50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment showed higher exposure for capecitabine, 5-DFUR, and FBAL than in those with normal renal function.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. However, capecitabine has been reported to cause mild to moderate dizziness, motor disability especially. Patients should be cautioned against driving or operating machinery until it is established that they do not become somnolent.

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

The overall safety profile of capecitabine is based on data from over 3000 patients treated with capecitabine as monotherapy or capecitabine in combination with different chemotherapy regimens in multiple indications. The safety profiles of capecitabine monotherapy for the metastatic breast cancer, metastatic colorectal cancer and adjuvant colon cancer populations are comparable.

The most commonly reported and/or clinically relevant treatment-related adverse drug reactions (ADRs) were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), hand-foot syndrome (palmar-plantar erythrodysesthesia), fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism.

ADRs considered by the investigator to be possibly, probably, or remotely related to the administration of Capecitabine are listed in table 4 for capecitabine given as monotherapy

and in table 5 for capecitabine given in combination with different chemotherapy regimens in multiple indications. The following headings are used to rank the ADRs by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Capecitabine Monotherapy:

Below lists ADRs associated with the use of capecitabine monotherapy based on a pooled analysis of safety data from three major studies including over 1900 patients (studies M66001, SO14695, and SO14796). ADRs are added to the appropriate frequency grouping according to the overall incidence from the pooled analysis.

Summary of related ADRs reported in patients treated with capecitabine monotherapy.

Infections and infestations

Common: Herpes viral infection, nasopharyngitis and lower respiratory tract infections.

Uncommon: Sepsis, urinary tract infection, cellulitis, tonsillitis, pharyngitis, oral candidiasis, influenza, gastroenteritis, fungal infection, infection and tooth abscess.

Neoplasm benign, malignant and unspecified

Uncommon: Lipoma.

Blood and lymphatic system disorders

Common: Neutropenia and anaemia.

Uncommon: Febrile neutropenia, pancytopenia, granulocytopenia, thrombocytopenia, leukopenia, haemolytic anaemia and international normalised ratio (inr) increased/prothrombin time prolonged.

Immune system disorders

Uncommon: Hypersensitivity.

Metabolism and nutrition disorders:

Very Common: Anorexia.

Common: Dehydration and weight decreased.

Uncommon: Diabetes, hypokalaemia, appetite disorder, malnutrition and hypertriglyceridaemia.

Psychiatric disorders

Common: Insomnia and depression.

Uncommon: Confusional state, panic attack, depressed mood and libido decreased.

Nervous system disorders

Common: Headache, lethargy, dizziness, parasthesia and dysgeusia.

Uncommon: Aphasia, memory impairment, ataxia, syncope, balance disorder, sensory disorder and neuropathy peripheral.

Very rare: Toxic leukoencephalopathy.

Eye disorders

Common: Lacrimation increased, conjunctivitis and eye irritation.

Uncommon: Visual acuity reduced and diplopia.

Rare: Lacrimal duct stenosis, corneal disorders, keratitis and punctate keratitis.

Ear and labyrinth disorders

Uncommon: Vertigo and ear pain.

Cardiac disorders

Uncommon: Angina unstable, angina pectoris, myocardial ischaemia/infarction, atrial fibrillation, arrhythmia, tachycardia, sinus tachycardia and palpitations.

Rare: Ventricular fibrillation, QT prolongation, Torsade de pointes, bradycardia and vasospasm.

Vascular disorders

Common: Thrombophlebitis.

Uncommon: Deep vein thrombosis, hypertension, petechiae, hypotension, hot flush and peripheral coldness.

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea, epistaxis, cough and rhinorrhoea.

Uncommon: Pulmonary embolism, pneumothorax, haemoptysis, asthma and dyspnoea exertional.

Gastrointestinal disorders

Very common: Diarrhoea, vomiting, nausea, stomatitis and abdominal pain.

Common: Gastrointestinal haemorrhage, constipation, upper abdominal pain, dyspepsia, flatulence and dry mouth.

Uncommon: Intestinal obstruction, ascites, enteritis, gastritis, dysphagia, abdominal pain lower, oesophagitis, abdominal discomfort, gastrooesophageal reflux disease, colitis and blood in stool.

Hepatobiliary disorders

Common: Hyperbilirubinemia and liver function test abnormalities.

Uncommon: Jaundice.

Rare: Hepatic failure and cholestatic hepatitis.

Skin and subcutaneous tissue disorders

Very common: Palmar-plantar erythro-dysaesthesia syndrome**

Common: Rash, Alopecia, Erythema, dry skin, pruritus, skin hyperpigmentation, rash macular, skin desquamation, dermatitis, pigmentation disorder and nail disorder.

Uncommon: Blister, Skin ulcer, rash, urticaria, photosensitivity reaction, palmar erythema, swelling face, purpura and radiation recall syndrome.

Rare: Cutaneous lupus erythematosus.

Very rare: Severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal necrolysis.

Musculoskeletal and connective tissue disorders

Common: Pain in extremity, back pain and arthralgia.

Uncommon: Joint swelling, bone pain, facial pain, musculoskeletal stiffness and muscular weakness.

Renal and urinary disorders

Uncommon: Hydronephrosis, urinary incontinence, haematuria, nocturia and blood creatinine increased.

Reproductive system and breast disorders

Uncommon: Vaginal haemorrhage.

General disorders and administration site conditions

Very common: Fatigue and asthenia.

Common: Pyrexia, oedema peripheral, malaise and chest pain.

Uncommon: Oedema, chills, influenza like illness, rigors and body temperature increased.

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

Capecitabine in combination therapy:

Below lists, ADRs associated with the use of capecitabine in combination with different chemotherapy regimens in multiple indications based on safety data from over 3000 patients. ADRs are added to the appropriate frequency grouping (Very common or Common) according to the highest incidence seen in any of the major clinical trials and are only added when they were seen in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy. Uncommon ADRs reported for Capecitabine in combination therapy are consistent with the ADRs reported for capecitabine monotherapy or reported for monotherapy with the combination medicinal product (in literature and/or respective summary of product characteristics).

Some of the ADRs are reactions commonly seen with the combination medicinal product (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin, hypertension seen with bevacizumab); however an exacerbation by capecitabine therapy can not be excluded.

Summary of related ADRs reported in patients treated with capecitabine in combination treatment in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to Capecitabine monotherapy.

Summary of related ADRs reported in patients treated with capecitabine combination therapy.

Infections and infestations

Common: Herpes zoster, urinary tract infection, oral candidiasis, upper respiratory tract infection, rhinitis, influenza, +infection and oral herpes.

Blood and lymphatic system disorders

Very common: +Neutropenia, +leucopenia, +anaemia, +neutropenic fever and thrombocytopenia.

Common: Bone marrow depression and +Febrile neutropenia.

Immune system disorders

Common: Hypersensitivity.

Metabolism and nutrition disorders:

Very common: Appetite decreased.

Common: Hypokalaemia, hyponatraemia, hypomagnesaemia, hypocalcaemia and hyperglycaemia.

Psychiatric disorders

Common: Sleep disorder and anxiety.

Nervous system disorders

Very common: Paraesthesia, dysaesthesia, peripheral neuropathy, peripheral sensory neuropathy, dysgeusia and headache.

Common: Neurotoxicity, tremor, neuralgia, hypersensitivity reaction and hypoaesthesia.

Eye disorders

Very common: Lacrimation increased.

Common: Visual disorders, dry eye, eye pain, visual impairment and vision blurred.

Ear and labyrinth disorders

Common: Tinnitus and hypoacusis.

Cardiac disorders:

Common: Atrial fibrillation and cardiac ischaemia/infarction.

Vascular disorders

Very common: Lower limb oedema, hypertension, +embolism and thrombosis.

Common: Flushing, hypotension, hypertensive crisis, hot flush and phlebitis.

Respiratory, thoracic and mediastinal disorders

Very common: Sore throat and dysaesthesia pharynx.

Common: Hiccups, pharyngolaryngeal pain and dysphonia.

Gastrointestinal disorders

Very common: Constipation and dyspepsia.

Common: Upper gastrointestinal haemorrhage, mouth ulceration, gastritis, abdominal distension, gastroesophageal reflux disease, oral pain, dysphagia, rectal haemorrhage, abdominal pain lower, oral dysaesthesia, paraesthesia oral, hypoaesthesia oral and abdominal discomfort.

Hepatobiliary disorders

Common: Hepatic function abnormal.

Skin and subcutaneous tissue disorders

Very common: Alopecia and nail disorder.

Common: Hyperhidrosis, rash erythematous, urticaria and night sweats.

Musculoskeletal and connective tissue disorders

Very common: Myalgia, arthralgia and pain in extremity.

Common: Pain in jaw, muscle spasms, trismus and muscular weakness.

Renal and urinary disorders

Common: Haematuria, proteinuria, creatinine renal clearance decreased and dysuria.

Rare: Acute renal failure secondary to dehydration.

General disorders and administration site conditions

Very common: Pyrexia, weakness, +lethargy and temperature intolerance.

Common: Mucosal inflammation, pain in limb, pain, chills, chest pain, influenza like illness, +fever, infusion related reaction, injection site reaction, infusion site pain and injection site pain.

Injury, poisoning and procedural complications

Common: Contusion.

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form **(form.heteroworld.com)** or by **Hetero Helpline No.180-020-01303.**

4.9 OVERDOSAGE

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 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 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/m^2 basis).

5. PHARMACOLOGICAL PROPERTIES

5.1 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, N^{5-10}-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 PHARMACODYNAMIC PROPERTIES

Microbiology

Capecitabine was superior to 5-FU/LV for objective response rate. The similarity of Capecitabine and 5-FU/LV was assessed by examining the potential difference between the two treatments. In order to assure that Capecitabine has a clinically meaningful survival effect, statistical analyses were performed to determine the percent of the survival effect of 5-FU/LV that was retained by Capecitabine. The estimate of the survival effect of 5-FU/LV was derived from a meta-analysis of ten randomized studies from the published literature comparing 5-FU to regimens of 5-FU/LV that were similar to the control arms. The method for comparing the treatments was to examine the worst case (95% confidence upper bound) for the difference between 5-FU/LV and Capecitabine, and to show that loss of more than 50% of the 5-FU/LV survival effect was ruled out. It was demonstrated that the percent of the survival effect of 5-FU/LV maintained was at least 61% and 10%.

5.3 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of 1255 mg/m^2 BID to cancer patients, capecitabine reached peak blood levels in about 1.5 hours (T_{max}) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of capecitabine with mean C_{max} and $AUC_{0-\alpha}$ decreased by 60% and 35%, respectively. The C_{max} and $AUC_{0-\alpha}$ 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 and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m^2/day. Over this range, the pharmacokinetics of Capecitabine 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 C_{max} and AUC of 5-FU was greater than 85%.

Distribution

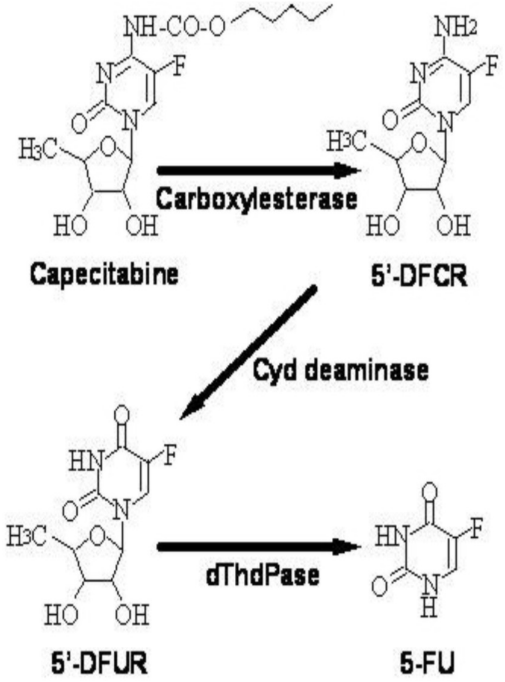
Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration-dependent. Capecitabine was primarily bound to human albumin

(approximately 35%). Capecitabine 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 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

Metabolic Pathway of capecitabine to 5-FU



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.

6. NONCLINICAL PROPERTIES

6.1 ANIMAL TOXICOLOGY OR PHARMACOLOGY

In repeat-dose toxicity studies, daily oral administration of capecitabine to cynomolgus monkeys and mice produced toxic effects on the gastrointestinal, lymphoid and haemopoietic systems, typical for fluoropyrimidines. These toxicities were reversible. Skin toxicity, characterised by degenerative/regressive changes, was observed with capecitabine.

Capecitabine was devoid of hepatic and CNS toxicities. Cardiovascular toxicity (e.g., PR- and QT-interval prolongation) was detectable in cynomolgus monkeys after intravenous administration (100 mg/kg) but not after repeated oral dosing (1379 mg/m^2/day).

A two-year mouse carcinogenicity study produced no evidence of carcinogenicity by capecitabine.

During standard fertility studies, impairment of fertility was observed in female mice receiving capecitabine; however, this effect was reversible after a drug-free period. In addition, during a 13-week study, atrophic and degenerative changes occurred in reproductive organs of male mice; however these effects were reversible after a drug-free period.

In embryotoxicity and teratogenicity studies in mice, dose-related increases in foetal resorption and teratogenicity were observed. In monkeys, abortion and embryolethality were observed at high doses, but there was no evidence of teratogenicity.

Capecitabine was not mutagenic in vitro to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). However, similar to other nucleoside analogues (i.e., 5-FU), capecitabine was clastogenic in human lymphocytes (in vitro) and a positive trend occurred in mouse bone marrow micronucleus tests (in vivo).

7. DESCRIPTION

CAPECITE 500 is supplied for oral administration, as a film coated tablet of Capecitabine. Each film coated tablet of CAPECITE 500 contains Capecitabine 500 mg.

8. PHARMACEUTICAL PARTICULARS

8.1 INCOMPATIBILITIES
Not Applicable

8.2 SHELF-LIFE
Refer Pack

8.3 PACKING INFORMATION
Refer Pack

8.4 STORAGE CONDITION AND HANDLING INSTRUCTIONS
Refer Pack

9. PATIENT COUNSELLING INFORMATION

Diarrhoea

Inform patients experiencing grade 2 diarrhoea (an increase of 4 to 6 stools/day or nocturnal stools) or greater or experiencing severe bloody diarrhoea with severe abdominal pain and fever to stop taking Capecitabine. Advise patients on the use of antidiarrheal treatments (e.g., loperamide) to manage diarrhoea.

Cardiotoxicity

Advise patients of the risk of cardiotoxicity and to immediately contact their healthcare provider or to go to an emergency room for new onset of chest pain, shortness of breath, dizziness, or light-headedness.

Dihydropyrimidine Dehydrogenase Deficiency

Advise patients to notify their healthcare provider if they have a known DPD deficiency. Advise patients if they have complete or near complete absence of DPD activity they are at an increased risk of acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by Capecitabine (e.g., mucositis, diarrhoea, neutropenia, and neurotoxicity).

Dehydration and Renal Failure

Instruct patients experiencing grade 2 or higher dehydration (IV fluids indicated < 24 hours) to stop taking Capecitabine immediately and to call their healthcare provider to correct the dehydration. Advise patients to not restart Capecitabine until rehydrated and any precipitating causes have been corrected or controlled.

Important Administration Instructions

Advise patients to swallow Capecitabine tablets whole with water within 30 minutes of a meal. Advise patients and caregivers not to crush or cut Capecitabine tablets. Advise patients if they cannot swallow Capecitabine tablets whole, to inform their healthcare provider.

Nausea

Instruct patients experiencing grade 2 nausea (food intake significantly decreased but able to eat intermittently) or greater to stop taking Capecitabine immediately and to contact their healthcare provider for management of nausea.

Vomiting

Instruct patients experiencing grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater to stop taking Capecitabine immediately and to contact their healthcare provider for management of vomiting.

Hand-and-Foot Syndrome

Instruct patients experiencing grade 2 hand-and-foot syndrome (painful erythema and swelling of the hands and/or feet and/or discomfort affecting the patients' activities of daily living) or greater to stop taking Capecitabine immediately and to contact their healthcare provider. Inform patients that initiation of symptomatic treatment is recommended and hand-and-foot syndrome can lead to loss of fingerprints, which could impact personal identification.

Stomatitis

Inform patients experiencing grade 2 stomatitis (painful erythema, edema or ulcers of the mouth or tongue, but able to eat) or greater to stop taking Capecitabine immediately and to contact their healthcare provider.

Fever and Neutropenia

Inform patients who develop a fever of 100.5°F or greater or other evidence of potential infection to contact their healthcare provider.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with Capecitabine and for 6 months after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Capecitabine and for 3 months after the last dose.

Lactation

Advise females not to breastfeed during treatment with Capecitabine and for 2 weeks after the last dose.

10. DETAILS OF MANUFACTURER

Refer Pack for manufacturer details.

MARKETED BY:

Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. D-4, Gala No. 1 to 3 &
11 to 13 Ground Floor, 101 to 106 & 111 to
116 First Floor, 201 to 206 & 211 to 216
2nd Floor, Pimplas, Dist. Thane,
Bhiwandi - 421 302,
Maharashtra, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER

Refer Pack for Permission/License details

12. DATE OF REVISION

Version 5.0; Dated 10th November 2025

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com