Capecitabine

Celabin™

500 mg Film-Coated Tablet
Cytostatic (ANTIMETABOLITE)

FORMULATION

Each film-coated tablet contains:
Capecitabine ..... 500 mg

PHARMACOLOGIC CATEGORY

Cytostatic (ANTIMETABOLITE)

PRODUCT DESCRIPTION

Capecitabine is a peach coloured, oblong shaped, biconvex, film-coated tablet, debossed with "500" on one side and plain on other side.

CLINICAL PHARMACOLOGY

Pharmacodynamics
Capecitabine is a tumor-activated antineoplastic agent (antimetabolite) belonging to the novel fluoropyrimidine carbamate class. It is an orally administered prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil (5-FU). Enzymes convert capecitabine to 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 transcription 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.

In a large randomized trial, combination of docetaxel and capecitabine produces a synergistic antitumor effect for the treatment of advanced breast cancer.

Pharmacokinetics
Capecitabine is rapidly and extensively absorbed unchanged from the gastrointestinal (GI) tract; on average at least 70% of an oral dose is absorbed. After oral administration of 1255 mg/m² two times a day 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 peak plasma concentration (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) decreased by 60% and 35%, respectively. The C_{max} and $AUC_{0-\infty}$ of 5-FU were also reduced by food by 43% and 21%, respectively. Food delayed T_{max} of both parent and f-FU by 1.5 hours.

The pharmacokinetics of capecitabine and its metabolites have been evaluated over a dose range of 500 to 3500 mg/m²/day. Over this range, the pharmacokinetics of capecitabine and its metabolite, 5'-deoxy-5-fluorocytidine (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.

Plasma protein binding of capecitabine and its metabolites is <60% and is not concentration dependent. Capecitabine is primarily bound to human albumin (~35%). Capecitabine has a low potential for pharmacokinetic interactions related to plasma protein binding.

Capecitabine has little pharmacologic activity until it is extensively metabolized enzymatically to 5-FU. In the liver, much of the compound is hydrolyzed by a 60 kDa carboxylesterase to 5'-DFCR. Cytidine deaminase, principally located in the liver and tumor tissue, subsequently converts 5'-DFCR to 5'-DFUR. Further metabolism of 5'-DFUR to the pharmacologically active agent 5-FU occurs mainly at the site of the tumor by thymidine phosphorylase (dThdPase), which has levels considerably higher in tumor tissues compared to normal tissues.

The enzyme dihydropyrimidine dehydrogenase hydrogenates 5-FU, the product of capecitabine metabolism to the much less toxic 5-fluoro-5,6-dihydro-fluorouracil (FUH_2). Dihydropyrimidinase cleaves to 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.

Capecitabine and its metabolites are predominantly excreted in the 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.

INDICATIONS

Capecitabine is indicated for the following conditions:

- **Colorectal Cancer**
  - Adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer when treatment with fluoropyrimidine therapy alone is preferred
  - First-line treatment of metastatic colorectal cancer when treatment with fluoropyrimidine therapy alone is preferred.
  - Treatment, in combination with oxaliplatin, of patients with metastatic colorectal cancer following failure of irinotecan-containing combination chemotherapy.

- **Breast Cancer**
  - Treatment, in combination with docetaxel, of patients with locally advanced or metastatic breast cancer after failure of prior anthracycline-containing chemotherapy
  - Treatment, as monotherapy, of patients with locally advanced or 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~~

DOSAGE AND ADMINISTRATION
Capecitabine is intended for long term administration unless clinically inappropriate. Capecitabine tablets should be swallowed whole with water **within 30 minutes after a meal.** Do not crush or cut capecitabine tablet. If progressive disease or intolerable toxicity is observed, treatment with capecitabine should be discontinued. The standard and reduced dose of capecitabine is calculated according to body surface area. (*see Table 1 and 2*)

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 that the neutrophil count drops below 1.0 x 10^9/L or that the platelet count drops below 75 x 10^9/L, treatment with capecitabine should be interrupted.

Patients should be carefully monitored for toxicity and doses of capecitabine should be modified as necessary to accommodate individual patient tolerance to treatment. (*see Table 3 and 4*)

Monotherapy:
Recommended Capecitabine Dose for Metastatic Colorectal Cancer, Adjuvant Colorectal Cancer, Metastatic Breast Cancer
- 1250 mg/m² administered orally 2 times a day (morning and evening; equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by 1 week rest period given for a total of 8 cycles

Combination Therapy:
Recommended Capecitabine Dose in Combination with Oxaliplatin for Metastatic Colorectal Cancer
- 1000 mg/m² two times a day for 2 weeks followed by 1 week rest period
- The first dose of capecitabine is given on the evening of day 1 and the last dose is given on the morning of day 15
- Given as a 3-weekly schedule, oxaliplatin is administered as 130 mg/m² intravenous infusion over 2 hours
- Premedication to maintain adequate anti-emesis should be started prior to oxaliplatin administration for patients receiving capecitabine plus oxaliplatin combination (*see oxaliplatin product information for dosage and administration*)

Recommended Capecitabine Dose in Combination with Docetaxel for Metastatic Breast Cancer
- 1250 mg/m² two times a day (morning and evening; equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by 1 week rest period
- Docetaxel 75 mg/m² is administered as 1-hour IV infusion on the first day of each 3-week cycle
- Premedication, according to docetaxel labeling, should be started prior to docetaxel administration for patients receiving capecitabine plus docetaxel combination (*see docetaxel product information for dosage and administration*)

Table 1. Standard and reduced dose calculations according to body surface area for starting Capecitabine dose of 1250 mg/m²

Dose Level 1250 mg/m² Two Times a Day				
Body Surface Area (m²)	Total Daily Dose* (mg)	Number of Capecitabine 500 mg Tablets to be Taken at Each Dose (Morning and Evening)	Reduced dose(75%) 950 mg/m²	Reduced dose(50%) 625 mg/m²
≤ 1.26	3000	3	2300	1600
1.27 to 1.38	3300	3	2600	1600
1.39 to 1.52	3600	3	2900	1900
1.53 to 1.66	4000	4	3000	2000
1.67 to 1.78	4300	4	3300	2000
1.79 to 1.92	4600	4	3600	2300
1.93 to 2.06	5000	5	3900	2600
2.07 to 2.18	5300	5	4000	2600
≥ 2.19	5600	5	4300	2900

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

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

Dose Level 1000 mg/m² Two Times a Day				
Body Surface Area (m²)	Total Daily Dose* (mg)	Number of Capecitabine 500 mg Tablets to be Taken at Each Dose (Morning and Evening)	Reduced dose(75%) 750 mg/m²	Reduced dose(50%) 500 mg/m²
≤ 1.26	2300	2	1600	1200
1.27 to 1.38	2600	2	2000	1200
1.39 to 1.52	2900	2	2200	1500
1.53 to 1.66	3200	2	2400	1600
1.67 to 1.78	3500	3	2600	1600
1.79 to 1.92	3600	3	2800	1800
1.93 to 2.06	4000	4	3000	2000
2.07 to 2.18	4300	4	3200	2100
≥ 2.19	4600	4	3500	2200

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

Dose Management Guidelines
Toxicity due to capecitabine administration may be managed by symptomatic treatment and/or modification of the dose (i.e., treatment interruption, dose reduction). Once the dose has been reduced, it should not be increased at a later time. Treatment can be continued at the same dose without reduction or interruption for toxicities that are considered by the treating physician to be unlikely to become serious or life threatening (e.g., alopecia, altered taste, nail changes). Doses of capecitabine that are omitted because of toxicity are not replaced nor restored.

Table 3. Criteria for Selected Clinical Toxicities Associated with Capecitabine Therapy*

Adverse Events	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Life threatening (Grade 4)
Diarrhea	2 to 3 stools/day > pretreatment	4 to 6 stools/day > pretreatment or nocturnal stools	7 to 9 stools/day > pretreatment or incontinence and malabsorption	> 10 stools/day > pretreatment, grossly bloody diarrhea or the need for parenteral support
Nausea	Able to eat reasonable intake of food	Significant decreased in intake of food but able to eat intermittently	No significant intake of food	- -
Vomiting	1 episode in 24 hours	2 to 5 episodes in 24 hours	6 to 10 episodes in 24 hours	> 10 episodes in 24 hours, dehydration, or need for parenteral support
Abdominal Pain	Pain but no treatment required	Pain controlled with non-opiates	Pain controlled with opiates	Uncontrollable pain
Hand-and-foot syndrome	Numbness, dysaesthesia or paresthesia, tingling, painless swelling, or erythema of the hands and/or feet that causes discomfort but does not disrupt normal activities of daily living	Painful erythema and swelling of the hands and/or feet that results in discomfort affecting the normal activities of daily living	Moist desquamation, ulceration, blistering, and severe pain of the hands and/or feet and/or severe discomfort that causes inability to work or perform activities of daily living	- -
Lymphopenia	Lymphocyte count 1500 to 1999/mm³	Lymphocyte count 1000 to 1499/mm³	Lymphocyte count 500 to 999/mm³	Lymphocyte count <500 to 500/mm³

* National Cancer Institute of Canada (NCIC) Common Toxicity Criteria were used except for hand-and-foot syndrome, which is defined according to a grading system incorporated by Roche and accepted by FDA.

- **Monotherapy**
  Capecitabine dose modification scheme is recommended for the management of adverse reaction.

Table 4. Recommended Dose Modifications of Capecitabine

Toxicity NCIC Grades *	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% 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

Combination Therapy
Dose modifications for toxicity when capecitabine is used in combination with other therapies should be made according to Table 4 above for capecitabine and according to the appropriate product information for the other agent/s.

If a treatment delay is indicated for either capecitabine or the other agent/s at the beginning of a treatment cycle, then administration of all agents should be delayed until the requirements for starting all drugs are met. On the other hand, if the treating physician considered the toxicities not to be related to capecitabine during a treatment cycle, capecitabine should be continued and the dose of the other agent adjusted accordingly.

If the other agent/s have to be discontinued permanently, then capecitabine treatment can be resumed when the requirements for restarting capecitabine are met.

Table 5. Docetaxel Dose Reduction Schedule in Combination with Capecitabine

Toxicity NCIC Grades*	Grade 2	Grade 3	Grade 4
1st appearance	Delay treatment until resolved to grade 0 to 1; Resume treatment with original dose of 75 mg/m² docetaxel	Delay treatment until resolved to grade 0 to 1; Resume treatment at 55 mg/m² of docetaxel	Discontinue treatment with docetaxel
2nd appearance	Delay treatment until resolved to grade 0 to 1; Resume treatment at 55 mg/m² of docetaxel	Discontinue treatment with docetaxel	- -
3rd appearance	Discontinue treatment with docetaxel	- -	- -
4th appearance	- -	- -	- -

* National Cancer Institute of Canada Common (NCIC) Toxicity Criteria were used except for hand-and-foot syndrome

Adjustment of Starting Dose in Special Populations

- **Renal Impairment**
  Adjust the dose of capecitabine based on the patient's creatinine clearance (Cockroft and Gault Equation, as shown below) at baseline.

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

Creatinine clearance for Females = 0.85 x male value

Creatinine clearance in SI units (mL/s) = 0.01667 x value obtained from above formula in mL/min

The starting dose adjustment recommended for patients with moderate renal impairment apply to both capecitabine monotherapy and capecitabine in combination with docetaxel. Subsequent dose adjustment is recommended as outlined in Tables 4 and 5 (depending on the regimen) if a patient develops a grade 2 to 4 adverse event.

Table 6. Recommended Capecitabine Dose Modifications for Renal Impairment

Stage	Creatinine Clearance (mL/min)	Capecitabine Dosage Adjustment
Mild	51 to 80	None
Moderate	30 to 50	Reduce to 75% of dose (from 1250 mg/m² to 950 mg/m²)
Severe	< 30	CONTRAINDICATED

Handling Precautions
- Care should be exercised in the handling of capecitabine.
- Capecitabine tablets should not be cut or crushed.
- The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of tablets.
- If powder from broken capecitabine tablets comes in contact with the skin, wash the skin immediately and thoroughly with soap and water.
- If capecitabine comes in contact with mucous membranes, flush thoroughly with water.
- Procedures for the proper handling and disposal of anticancer drugs should be implemented.

CONTRAINDICATIONS

- Hypersensitivity to capecitabine, 5-FU or to any of the excipients of the product
- History of severe and unexpected reactions to fluoropyrimidine therapy
- Patients with known dihydropyrimidine dehydrogenase (DPD) deficiency
- Patients with severe renal impairment (creatinine clearance below 30 mL/min)
- Patients with severe hepatic impairment
- Patients with severe leucopenia, neutropenia (neutrophil counts <1.5 x 10^9/L), or thrombocytopenia (thrombocyte counts <100 x 10^9/L)
- Treatment with sorivudine or its chemically related analogues, such as brivudine
- Pregnant or breastfeeding women

WARNINGS AND PRECAUTIONS

WARNING: CAPECITABINE-WARFARIN INTERACTION
Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response [International Normalized Ratio (INR) or prothrombin time (PT)] monitored frequently in order to adjust the anticoagulant dose accordingly. A clinically important Capecitabine - Warfarin drug interaction was demonstrated in a clinical pharmacology trial. Altered coagulation parameters and/ or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Postmarketing reports have shown clinical significant increases in prothrombin time (PT) and INR in patients who were stabilized on anticoagulants at the time capecitabine was introduced. 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. Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy

General
Patients receiving therapy with capecitabine should be monitored by a physician experienced in the use of cancer chemotherapeutic agents.

Dose-limiting toxicities include diarrhea, abdominal pain, nausea, stomatitis, and hand-and-foot syndrome. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced.

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. The median time to first occurrence of grade 2 to 4 diarrhea was 34 days (range from 1 to 369 days) following initiation of capecitabine therapy for metastatic breast or colorectal cancer and the median duration of grade 3 to 4 diarrhea was 5 days.

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. Following a recurrence of grade 2 diarrhea or occurrence of any grade 3 or 4 diarrhea, subsequent doses of capecitabine should be decreased. Standard antidiarrheal treatments (e.g., loperamide) should be initiated, as medically appropriate, as early as possible. Dose reduction should be applied as necessary (*see Dosage and Administration*).

Necrotizing enterocolitis (typhlitis) has been reported.

Dehydration
Patients with anorexia, asthenia, nausea, vomiting or diarrhea may rapidly become dehydrated. Dehydration may also cause acute renal failure which can be fatal. They should be prevented or corrected at the onset. Capecitabine tablets should be immediately interrupted and the dehydration corrected if Grade 2 (or higher) dehydration occurs. 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 (*see Dosage and Administration*).

Mucocutaneous and Dermatologic Toxicity
Severe adverse drug reactions that may be fatal such as Stevens-Johnsons syndrome and Toxic Epidermal Necrolysis (TEN) can occur in patients treated with capecitabine. If patients experience these severe reactions possibly attributable to treatment with capecitabine, then the drug should be permanently discontinued.

Hand-and-foot syndrome, also called palmar-plantar erythrodysesthesia, is a cutaneous toxicity that is a side effect of some types of chemotherapy. 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.

When patients experience grade 2 or grade 3 hand-foot syndrome, capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Subsequent doses of capecitabine should be decreased following grade 3 hand-foot syndrome. If capecitabine and cisplatin are used in combination, the use of vitamin B_6 (pyridoxine) is not advised for symptomatic or secondary prophylactic treatment of hand-foot syndrome because of published reports that it may decrease the efficacy of cisplatin.

Cardiotoxicity
Myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiographic changes (including very rare cases of QT prolongation) has been associated with fluoropyrimidine therapy and these adverse reactions may be increased in patients with a prior history of coronary artery disease. Patients should be monitored carefully during capecitabine therapy.

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

Hyperbilirubinemia
Grade 3 to 4 hyperbilirubinemia has been reported in patients receiving capecitabine. If drug-related grade 2 to 4 elevations in bilirubin occur, administration of capecitabine should be immediately interrupted until the hyperbilirubinemia decreases to ≤ 3 x upper limit of normal (ULN). Following grade 3 or 4 hyperbilirubinemia, subsequent doses of capecitabine should be decreased (*see Dosage and Administration*)

Hematologic Effects
In 875 patients with either metastatic breast or colorectal cancer who received a dose of 1250 mg/m² administered two times a day as monotherapy for 14 days followed by a 7-day rest period, 3.2%, 1.7%, and 2.4% of patients had grade 3 or 4 neutropenia, thrombocytopenia or decreases in hemoglobin, respectively.

Capecitabine should not be taken by patients with baseline neutrophil counts of <1.5 x 10^9/L and/or thrombocyte counts of <100 x 10^9/L.

Nausea and Vomiting
Patients experiencing ≥ grade 2 nausea or vomiting should be instructed to stop taking capecitabine immediately. Initiation of symptomatic treatment is recommended.

Special Populations
Exercise caution in patients with the following conditions:
- Pre-existing hypo- or hypercalcemia, as capecitabine may cause hypo- or hypercalcemia
- Central or peripheral nervous system disease (e.g., brain metastasis or neuropathy)
- Diabetes mellitus or electrolyte disturbances, as these may be aggravated during capecitabine treatment

Carcinogenicity, Mutagenicity, Impairment of Fertility
Adequate studies investigating the carcinogenic potential of capecitabine 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 mutations in bacteria but was not clastogenic *in vivo* to mouse bone marrow (micronucleus test). 5-FU causes mutations in bacteria and yeast. 5-FU also causes chromosomal abnormalities in the mouse micronucleus test *in vivo*.

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.

Hepatic impairment
Though there are no data on the safety and efficacy of capecitabine in patients with severe hepatic impairment, patients taking capecitabine with mild to moderate liver dysfunction regardless of the presence or absence of liver metastasis should be carefully monitored. Treatment with capecitabine should be interrupted if there is a treatment-related elevations in bilirubin (>3.0 x ULN) or aminotransferases (ALT, AST; >2.5 x ULN). Treatment may resume when bilirubin decreases to ≤3.0 x ULN or hepatic aminotransferases decrease to ≤2.5 x ULN.

Renal Impairment
There is an increase in adverse reactions in patients with moderate renal impairment (creatinine clearance of 30-50 mL/min) compared to the overall population. Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse reactions while those with moderate renal impairment at baseline require dose reduction. Prompt interruption of therapy with subsequent dose adjustments is recommended if a patient develops a grade 2-4 adverse event.

Ophthalmologic complications
Patients, especially those with prior history of eye disorders, should be carefully monitored for opthalmological complications such as corneal disorders and keratitis.

Excipient
Anhydrous lactose is an excipient of this product. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Effects on Ability to Drive or Use Machines
Though it may cause dizziness, fatigue and nausea, capecitabine has minor or moderate influence on the ability to drive and use machines

DRUG INTERACTIONS

Coumarin-derivative Anticoagulants: Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon (*see Boxed Warning*). The dose of these agents may need to be reduced when administered concomitantly with capecitabine.

Phenytoin: Some patients receiving capecitabine and phenytoin had toxicity associated with elevated phenytoin levels. The level of phenytoin should be carefully monitored in patients taking capecitabine and phenytoin dose may need to be reduced.

Leucovorin: The antineoplastic activity of fluorouracil, the active drug of capecitabine, is potentiated by the addition of leucovorin that may also increase its toxicity. There have been reports of death due to severe enterocolitis, diarrhea and dehydration in geriatric patients receiving weekly regimen of leucovorin and fluorouracil combination.

Folinic Acid: Though folinic acid has no major effect on capecitabine's pharmacokinetics, it may, however, enhance capecitabine's toxicity. Capecitabine, when taken alone, has a maximum tolerated dose (MTD) of 3000 mg/m² daily whereas it is only 2000 mg/m² daily when combined with 30 mg twice a day oral folinic acid.

Sorivudine and analogues: Dihydropyrimidine dehydrogenase is an enzyme that converts fluorouracil into its much less toxic form. Sorivudine inhibits dihydropyrimidine dehydrogenase and this result to increased toxicity of capecitabine. Therefore, capecitabine must not be administered together with sorivudine or its chemically related analogues, such as brivudine. Wait for 4 weeks after ending treatment with sorivudine or its analogues before starting with capecitabine.

Antacid: Antacids containing aluminum hydroxide and magnesium hydroxide cause an increase in plasma concentration of capecitabine and one of its metabolite, 5'-deoxy-5-fluorocytidine.

Allopurinol: Allopurinol decreases the efficacy of fluorouracil. Thus, concomitant administration of capecitabine and allopurinol should be avoided.

Interferon alpha: Interferon alpha may enhance capecitabine toxicity because capecitabine, when taken alone, has a maximum tolerated dose (MTD) of 3000 mg/m² daily whereas it is only 2000 mg/m² daily when combined with interferon alpha.

Radiotherapy: The MTD of capecitabine alone using intermittent regimen is 3000 mg/m² daily, whereas, when combined with radiotherapy for rectal cancer, the MTD of capecitabine is 2000 mg/m² daily using either continuous schedule or given daily (Monday-Friday) during a 6-week course of radiotherapy.

Oxaliplatin: Free platinum or total platinum occurred when capecitabine is administered in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab.

Bevacizumab: When given in the presence of oxaliplatin, bevacizumab causes no clinically significant effect on the pharmacokinetic parameters of capecitabine.

Food interaction: Food decreases the rate of capecitabine absorption. However, based on current safety and efficacy data, the drug is administered with food.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Women of childbearing potential
Women should be advised to avoid becoming pregnant while receiving capecitabine. If in case the patient got pregnant, the potential hazard to the fetus must be explained.

Pregnancy Category D
There are no data on the safety of capecitabine in pregnant women; however, in animal studies, it caused embryolethality and teratogenicity that are expected effects of fluoropyrimidine derivatives. Thus, pregnancy should be avoided while receiving treatment with capecitabine.

Lactation
In an animal study, capecitabine and its metabolites were found in the milk of lactating mice. In human breast milk, however, it is unknown. Hence, breast-feeding should be discontinued while receiving treatment with capecitabine.

Pediatric (<18 years old)
There is no data on the use of capecitabine in children; safety and efficacy in pediatric patients have not been established.

Geriatric (≥ 80 years old)
Geriatric patients may experience increased frequency and severity of the toxic effects of capecitabine and its metabolites. Patients aged ≥ 80 years old that are being treated for metastatic breast cancer or metastatic colorectal cancer experience a greater incidence of grade 3 or 4 adverse effect, in particular, GI effects or severe hand-foot syndrome. Physicians should exercise caution in monitoring the effects of capecitabine in the elderly. Insufficient data are available to recommend dose adjustment of capecitabine in geriatric patients.

UNDESIRABLE EFFECTS

The most common adverse effects that were reported with capecitabine use are diarrhea, nausea, vomiting, abdominal pain, stomatitis, hand-and-foot syndrome, fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction on those with preexisting compromised renal function and thrombosis or embolism. Other adverse effects of capecitabine used both as monotherapy or in combination with other chemotherapy regimens are:

Infections and infestations: Herpes viral infection, nasopharyngitis, lower respiratory tract infection, upper respiratory tract infection, sepsis, urinary tract infection, cellulitis, tonsillitis, pharyngitis, oral candidiasis, oral herpes, influenza, gastroenteritis, fungal infection, infection, tooth abscess, rhinitis, viral infection, bronchitis, bronchopneumonia, pneumonia, otitis media, superinfection

Neoplasms benign, malignant and unspecified: Lipoma, solar keratoses

Blood and lymphatic system disorders: Neutropenia, anemia, febrile neutropenia, pancytopenia, granulocytopenia, thrombocytopenia, leucopenia, hemolytic anemia, INR increased, prothrombin time prolonged, bone marrow depression, hyperbilirubinemia, jaundice, lymphoedema, lymphopenia, coagulopathy, neutropenic sepsis, agranulocytosis

Immune system disorders: Hypersensitivity, asthma, urticaria, swelling face, Stevens-Johnson syndrome, drug hypersensitivity, face edema, skin reaction, bronchospasm, food allergy

Endocrine disorders: Hypothyroidism, hirsutism

Metabolism and nutrition disorders: Anorexia, edema, dehydration, decreased appetite, weight increased/decreased, diabetes, hypokalemia, appetite disorder, malnutrition, hypertriglyceridemia, hypokalemia, hyponatremia, hypomagnesemia, hypocalcemia, hyperglycemia, lower limb edema, peripheral edema, thirst, fluid retention, food intolerance, diabetes control impaired

Psychiatric disorders: Insomnia, depression, confusional state, panic attack, depressed mood, libido decreased, sleep disorder, anxiety, dysphonia, mood alteration, irritability, aphasia, dysarthria, mental impairment, psychiatric symptom, psychogenic disorder

Nervous system disorders: Headache, lethargy, dizziness, paresthesia, dysesthesia, dysgeusia, ageusia, aphasia, memory impairment, ataxia, syncope, balance disorder, sensory disorder, peripheral neuropathy, peripheral sensory neuropathy, neurotoxicity, tremor, neuralgia, hypoesthesia, visual acuity reduced, diplopia, blurred vision, oral dysesthesia, oral paresthesia, oral hypoesthesia, muscular weakness, trismus, gait disturbance, sedation, encephalopathy, abnormal coordination, balance disorder, cerebrovascular accident, polyneuropathy, migraine, hepatic coma, facial palsy, myoclonus, peroneal nerve palsy, amnesia, personality change

Eye disorders: Lacrimation increased, conjunctivitis, eye irritation, visual disorders, dry eye, eye pain, visual impairment, keratoconjunctivitis, lacrimal duct stenosis, cataract, corneal disorder, keratitis, punctuate keratitis

Ear and labyrinth disorders: Vertigo, ear pain, tinnitus, hypoacusis, deafness, ear discomfort

Cardiac disorders: Angina unstable, angina pectoris, myocardial ischemia, atrial fibrillation, arrhythmia, tachycardia, sinus tachycardia, palpitation, dyspnea, exertional dyspnea, chest pain, bradycardia, ventricular extrasystoles, extrasystoles, myocarditis, pericardial effusion, supraventricular tachycardia, chest discomfort, orthopnea, cardiomyopathy, ventricular fibrillation, QT prolongation, Torsades de pointes

Vascular disorders: Thrombophlebitis, deep vein thrombosis, hypertension, hypotension, hot flush, flushing, peripheral coldness, embolism, thrombosis, epistaxis, hemoptysis, rectal hemorrhage, skin ulcer, venous thrombosis, hemorrhage, hemorrhagic diarrhea, venous phlebitis, thrombophlebitis, orthostatic hypotension, hemorrhoids, hematoma, varicose vein, transient ischemic attack, cushingoid, vasospasm

Respiratory, thoracic and mediastinal disorders: Cough, rhinorrhea, pulmonary embolism, pneumothorax, pharynx dysesthesia, pharyngolaryngeal pain, pharyngeal disorder, non-cardiac chest pain, pleural effusion, respiratory distress, laryngitis, increased sputum production, nasal ulcer, pleural disorder, sneezing

Gastrointestinal disorders: Sore throat, hiccup, gastrointestinal hemorrhage, constipation, upper/ lower abdominal pain, dyspepsia, flatulence, dry mouth, intestinal obstruction, enteritis, gastritis, dysphagia, esophagitis, abdominal discomfort, gastroesophageal reflux disease, colitis, blood in stool, upper gastrointestinal hemorrhage, mouth ulceration, abdominal distention, oral pain, gastrointestinal motility disorder, oral discomfort, upper gastrointestinal inflammatory disorders, ileus, proctalgia, gastric ulcer, toxic dilatation of intestine, gastroenteritis, necrotizing enterocolitis, esophageal ulcer, fecal abnormality, tongue disorder, incisional hernia, painful swallowing, melena

Hepatobiliary disorders: Ascites, abnormal hepatic function, hepatic fibrosis, hepatitis, hepatic failure, hepatotoxicity, hepatomegaly, hepatic pain, fatty liver, bile duct stone, hepatitis cholestatic

Skin and subcutaneous tissue disorders: Petechiae, rash, alopecia, erythema, dry skin, pruritus, skin hyperpigmentation, rash macular, skin desquamation, dermatitis, pigmentation disorder, nail disorder, photosensitivity reaction, palmar erythema, purpura, skin discoloration, rash erythematous, nail discoloration, onycholysis, idiopathic thrombocytopenia purpura, skin lesion, ecchymoses, hyperkeratosis, intertrigo, rosacea, scab, skin exfoliation, skin fissures, solar keratosis

Musculoskeletal and connective tissue disorders: Pain in extremity, back pain, arthralgia, joint swelling, bone pain, musculoskeletal stiffness, myalgia, pain in jaw, muscle spasms, chills, arthritis, neck pain, calcaneal spur, cutaneous lupus erythematosus

Renal and urinary disorders: Hydronephrosis, urinary incontinence, hematuria, nocturia, proteinuria, dysuria, renal impairment, acute renal failure, urinary tract disorder, chromaturia, urinary retention, polyuria

Reproductive system and breast disorders: Genital pruritus, intermenstrual bleeding, balanoposthitis, vaginal pain, nipple disorder, premenstrual tension syndrome, vaginal hemorrhage

General disorders and administration site conditions: Pain, facial pain, pyrexia, lethargy, malaise, influenza-like illness, temperature intolerance, mucosal inflammation, infusion related reaction, hyperhidrosis, collapse, mass, fibrosis, cachexia, sudden death unexplained, crackles

Investigations: Blood creatinine increased, creatinine renal clearance decreased, body temperature increased, prothrombin level decreased, blood pressure increased

Injury, poisoning and procedural complications: Phlebitis, injection site reaction, infusion site pain, injection site pain, blister, overdose, radiation recall syndrome, toxic epidermal necrolysis, injection site infection, contusion, scratch

Surgical and medical procedures: paronychia drainage, postoperative complications, wound drainage increased

OVERDOSE AND MANAGEMENT

Acute lethal dose of capecitabine in humans is not known. However, symptoms of overdose may include nausea, vomiting, diarrhea, mucositis, gastrointestinal irritation and bleeding, and bone marrow depression. Severe hand-foot syndrome, mucositis, and diarrhea have been experienced by patients receiving capecitabine 1657 mg/m² daily (as 2 divided doses) in a continuous daily regimen for at least 6 weeks.

Since there is no known antidote for capecitabine overdose, management consists of discontinuance of the drug and initiation of supportive measures appropriate for the type of toxicity observed. 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.

STORAGE CONDITIONS

Store at temperatures not exceeding 30°C.

Keep the product out of sight and reach of children.