

\*Adjustment of Starting Dose in Special Populations: Hoak Impairment: In patientd with mild to moderate hepatic dysfunction due to liver metastases, no starting dose adjustment is necessary however, patients should be carefully mediated. Patients with severe hepatic dysfunction have not been studied.

Renal Important : Insufficient data are available in patients with renal impairment to provide a dosage recommendation.

Geriatric population: The elderly may be pharmacodynamically more sensitive to the toxic effects of 5-FU and therefore, physician should exercise caution in monitoring the effect of Capecitabine in the elderly. Insufficient data are available to provide a dosage recommendation.

**Presentation** : Capecitabine 500mg tablets are available in the carton containing blister of 10 tablets.

**Storage**: Store protected from light & moisture at a temperature not exceeding 30°C.

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

Rx  
**Capecitabine Tablets IP 500mg**  
**CAPEKAST™**

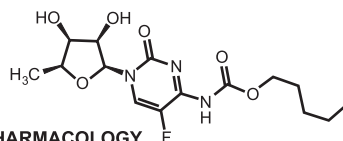
**COMPOSITION :**

Each film coated tablet contains :  
Capecitabine IP 500 mg.  
Excipients qs  
Colour : Red Oxide of Iron.

**DESCRIPTION :**

Capecitabine is a fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered prodrug of 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine which is converted to 5-fluorouracil.

The chemical name for capecitabine is 5'-deoxy-5-fluoro-N-[(pentyloxy) carboy]-cytidine and has a molecular weight of 359.35. Capecitabine has the following structural formula :



**CLINICAL PHARMACOLOGY**

Capecitabine is relatively non-cytotoxic in vitro. This drug is enzymatically converted to 5 fluorouracil (5-FU) in vivo.

**PHARMACOKINETICS**

**In Colorectal Tumors and Adjacent Healthy Tissue**

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.

**Human Pharmacokinetics**

The pharmacokinetic of capecitabine and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m<sup>2</sup>/day. Over this range, the pharmacokinetic of capecitabine and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUC<sub>0-24</sub> of 5'-DFIJR 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 elimination half-life of both parent capecitabine and 5-FU was about 1 hour. The inter-patient variability in the C<sub>max</sub> and A<sub>i</sub>-J<sub>C</sub> of 5-FU was greater than 85%.

Following oral administration of 825 mg/m<sup>2</sup> capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower C<sub>max</sub> and 24% lower AUC for capecitabine than the Caucasian patients (n=22). Japanese patients had also about 25% lower C<sub>max</sub> and 34% lower AUC for 5-FU 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).

**INDICATIONS AND USAGE**

Capecitabine is 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.

**CONTRAINDICATIONS**

Capecitabine is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil.

**PRECAUTIONS**

A physician experienced in the use of cancer chemotherapeutic agents should monitor patients receiving therapy with Capecitabine. Most adverse events are reversible and do not need to result in discontinuation, though doses may need to be withheld or reduced.

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**Hand-and-Foot Syndrome:** Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced amt erythema) may ems. If grade 2 or 3 hand-end-foot syndrome occurs, administration of Capecitabine should be interrupted until the event resolve or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of Capecitabine should be decreased.

**Cardiac:** There has been cardiotoxicity associated with tiourinatedpylmidine therapy, including myocardial infarction, angina, dysrhythmias, cardiogenic shock, sudden death and electrocardiograph changes. These adverse events may be more common in patients with a prior history of coronary artery disease. **Hepatic Ins& fidoncy:** 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.

**Hyperbilirubinemia:** If drug related grade 2-4 elevations in bilirubin occur, administration of Capecitabine should be immediately interrupted until the Hyperbilirubinemia resolves or decreases in intensity to grade 1.

**Renal Insufficiency** There is little experience in patients with renal impairment. Physicians should exercise caution when Capecitabine is administered.

**Hematologic:** Capecitabine can lead neutropenia, thrombocytopenia and decreases in hemoglobin. **Carcinogenesis and Mutagenesis:** Long-term studies in animals to evaluate the carcinogenic potential of Capecitabine have not been conducted. Capecitabine has not been shown to be mutagenic in vitro or in vivo.

**Impairment of Fertility:** Capecitabine causes a decrease in fertility by disturbing the estrus. In male mice, Capecitabine causes degenerative changes in the testes, including decreases in the number of spermatocytes and spermatids.

**Nursing Women:** It is not known whether the 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, it is recommended that nursing be discontinued when receiving Capecitabine therapy.

**Pediatric Use:** The safety and effectiveness of Capecitabine in children < 18 years of age have not been established.

**Geriatric Use:** Patients > ten years old may experience a greater incidence of gastrointestinal grade 4 or 4 adverse events. Physicians should pay particular attention to monitoring the adverse effects of Capecitabine in the elderly.

**Drug-Food Interaction:** Since current safety and efficacy data are based upon administration of Capecitabine with food, it is recommended that Capecitabine be administered with food.

#### WARNINGS

**Coagulopathy:** Altered coagulation parameters and/or bleeding have been reported in patients taking Capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon.

**Diarrhea:** Capecitabine can induce diarrhea, sometimes severe. Necrotizing enterocolitis has been reported with Capecitabine usage. **Pregnancy:** Capecitabine may cause fetal harm when given to a pregnant woman. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Capecitabine.

#### DRUG INTERACTIONS

**Antacid:** Aluminum hydroxide- and magnesium hydroxide-containing antacid cause a small increase in plasma concentration of Capecitabine and one metabolite (5'-DFCR).

**Coumarin Anticoagulants:** Patients taking coumarin derivative anticoagulants concomitantly with Capecitabine should be monitored regularly for alterations in their coagulation parameters.

**Phenyloin:** The level of phenytoin should be carefully monitored in patients taking Capecitabine and phenytoin dose may need to be reduced. **Leucovorin:** The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by Leucovorin.

#### Side Effects

Adverse events occurring in >5% of patients taking Capecitabine are as follows.

**Gastrointestinal:** Diarrhea, nausea, vomiting, stomatitis, abdominal pain, constipation and dyspepsia. **Skin and subcutaneous:** Hand-and-foot

Syndrome, dermatitis and nail disorder. **General:** Fatigue, pyrexia, pain in limb

**Neurological:** Paresthesia, headache, dizziness and insomnia. **Metabolism:** Anorexia and dehydration

**Eye:** Eye irritation **Musculoskeletal:** Myalgia

**Cardiovascular.** Edema, blood, neutropenia, thrombocytopenia, anemia, lymphopenia **Hepatobiliary.** Hyperbilirubinemia

#### OVER DOSAGE

The anticipated manifestations of acute overdose are nausea, vomiting, diarrhea, gastrointestinal irritation and bleeding, and bone marrow depression. It should be managed with supportive medical interventions aimed at correcting the presenting clinical manifestations. Although no clinical experience has been reported, dialysis may be of benefit in reducing circulating concentrations of 5-DFUR, a low-molecular weight metabolite of the parent compound.

#### DOSAGE AND ADMINISTRATION

The recommended dose of Capecitabine is 2500 mg/m<sup>2</sup> administered orally daily with food for 2 weeks followed by a 1-week rest period given as 3 week cycles. The Capecitabine daily dose should be given orally in two divided doses (approximately 12 hours apart) at the end of a meal. Capecitabine tablets should be swallowed with water. The following table displays the total daily dose by body surface area and the number of tablets to be taken at each dose.

Capecitabine Dose Calculation According to Body Surface Area			
Dose level 255 mg/m <sup>2</sup> /day Surface Area		Number of tablets to be taken at each dose (morning and evening)	
Surface Area (m <sup>2</sup> )	Total Daily* Dose (mg)	150mg	500mg
< /=1.24	3000	0	3
1.25-1	3300	1	3
1.37-1.51	3600	2	3
1.52-1.64	4000	0	4
1.65-1.76	4300	1	4
1.65-1.76	4600	2	4
1.92-2.04	5000	0	5
2.05-2.17	5300	1	5
> /=2.18	5600	2	5

Total Daily dose divided by 2 to allow equal morning and evening doses.

**Dose Modification guidelines:** Patients should be carefully monitored for toxicity. Toxicity due to Capecitabine administration may be managed by symptomatic treatment, dose interruptions and adjustment of Capecitabine dose. Once dose has been reduced it should not be increased at a later time

Recommended Dose Modifications			
Toxicity Grades	NCIC	During a Course of Therapy	Dose Adjustment for Next Cycle (% of starting dose)
Grade 1		Maintain dose level	Maintain dose level
Grade 2			
-1. appearance		Interrupt until resolved to grade 0-1	100%
-2 <sup>a</sup> appearance			75%
-3. appearance		Interrupt until resolved for a	50%
-4. appearance		Discontinue treatment permanently	
Grade 3			
-1. appearance		Interrupt until resolved to grade 0-1	75%
-2. appearance		Interrupt until resolved to grade 0.1	50%
-r appearance		Discontinue treatment permanently	
Grade 4			
-1. 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.