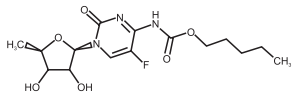
CAPETIZ 150/500
Capecitabine Tablets USP 150 mg / 500 mg

Rx only
COMPOSITION
CAPETIZ™ 150
Capecitabine Tablets USP 150 mg
Each film coated tablet contains:
Capecitabine USP 150mg
Excipients q.s
Colours: Iron Oxide of Red and Titanium Dioxide USP

CAPETIZ™ 500
Capecitabine Tablets USP 500 mg
Each film coated tablet contains:
Capecitabine USP 500mg
Excipients q.s
Colours: Iron Oxide of Red and Titanium Dioxide USP



DESCRIPTION
CAPETIZ is a fluoropyrimidine carbamate with Antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5' -DFUR) which is converted to 5-fluorouracil.
The chemical name for CAPETIZ is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and has a molecular weight of 359.35.

CLINICAL PHARMACOLOGY
CAPETIZ is relatively non-cytotoxic in vitro. This drug is enzymatically converted to5 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 0.9to 8.0). These ratios have not been evaluated in breast cancer patients or compared to 5-FU infusion.

Human Pharmacokinetlcs
The pharmacokinetics of CAPETIZ 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 AUG 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 ¾ of an hour. The inter-patient variability in the Cmax and AUC of 5-FU was greater than 85%. Following oral administration of 825 mg/m2 Capecitabine twice daily for 14 days.Japanese patients (n=18) had about 36% lower Cmax and 24% lower AUG for Capecitabine than the Caucasian patients (n=22). Japanese patients had also about 25% lower Cmax and 34% lower AUC for FBAL than the Caucasian patients. The clinical significance of these differences is unknown. No significant differences occurred in the exposure to other metabolites (5'-DFCR, 51-DFUR, and5-FU).

INDICATIONS AND USAGE
CAPETIZ is indicated for the treatment of patients with meatastatic 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
CAPETIZ 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 CAPETIZ. Most adverse events are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced.
Hand-and-Foot Syndrome: Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) may occur. If grade 2 or 3 hand-and-foot syndrome occurs, administration of CAPETIZ 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 fluorinatedpyrimidine 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 Insufficiency: Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when CAPETIZ 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 CAPETIZ 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 CAPETIZ is administered.

Hematologic: CAPETIZ lead neutropenia, thrombocytopenia and decreases in hemoglobin.

Carcinogenesis and Mutagenesls: Long - term studies in animals to evaluate the carcinogenic potential of CAPETIZ have not been conducted. Capecitabine has not been shown to be mutagenic in vitro or in vivo.

Impairment of Fertllity: CAPETIZ causes a decrease in fertility by disturbing the estrus. In male mice, CAPETIZ 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 CAPETIZ in persons < 18 years of age have not been established.

Geriatric Use: Patients ≥ / = 80 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 CAPETIZ with food, it is recommended that CAPETIZ be administered with food.

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

Diarrhea: CAPETIZ can induce diarrhea, sometimes severe. Necrotizing enterocolitis has been reported with CAPETIZ usage.

Pregnancy: CAPETIZ 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 CAPETIZ.

DRUG INTERACTIONS
Antacid: Aluminum hydroxide- and magnesium hydroxide-containing antacid cause a small increase in plasma concentration of CAPETIZ and one metabolite (5'-DFCR).
Coumarin Anticoagulants: Patients taking coumarinderivative anticoagulants concomitantly with CAPETIZ should be monitored regularly for alterations in their coagulation parameters.

Phenytoln: The level of phenytoin should be carefully monitored in patients taking CAPETIZ 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 CAPETIZ 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

Size: 100x182 mm

Neurological: Paresthesia, headache, dizziness and insomnia.

Metabolism: Anorexia and dehydration

Eye: Eye irritation

Musculoskeletal: Myalgia

Cardiovascular: Edema, blood, neutropenia, thrombocytopenia, anemia, lymphopenia

Hepatobiliary: Hyperbillirubinemia

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 5-0FUR, a low-molecular weight metabolite of the parent compound.

DOSAGE AND ADMINISTRATION

The recommended dose of CAPETIZ is 2500 mg/m' administered orally daily with food for 2 weeks followed by a 1-week rest period given as 3 week cycles. The CAPETIZ daily dose should be given orally in two divided doses (approximately 12 hours apart) at the end of a meal. CAPETIZ 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.

*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 CAPETIZ administration may be managed by symptomatic treatment, dose interruptions and adjustment of CAPETIZ dose. Once dose has been reduced it should not be increased at a later time.

*National Cancer Institute of Canada Common Toxicity Criteria were used except for the Hand-and-Foot Syndrome.

Adjustment of Starting Dose In Special Populations:

Hepatic Impairment: In patient with mild to moderate hepatic dysfunction due to liver metastases, no starting dose adjustment is necessary; however, patients should be carefully monitored. 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 bepharmacodynamically more sensitive to the toxic effects of 5-Fu and therefore, physician should exercise caution in monitoring the effects of Capecitabine in the elderly. Insufficient data are available to provide a dosage recommendation.

Recommended Dose Modifications		
Toxicity NCIC Grades*	**During a Course of Therapy**	**Dose Adjustment for Next Cycle (%of starting dose)**
Grade1	Maintain dose level	Maintain dose level
Grade2		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance	Interruot until resolved to grade 0-1	75%
-3rd appearance	Interrupt until resolved to grade 0-1	50%
-4th appearance	Discontinue treatment permanently	
Grade 3		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance	Interrupt until resolved to grade 0-1	50%
-3rd appearance	Discontinue treatment permanently	
Grade 4		
-1st appearanc	Discontinue permanently or it physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade0-1	50%

STORAGE

Store below 30° C

SHELF LIFE

24Months

HOW SUPPLIED

CAPETIZ 150 supplied in a bottle of 60 tablets packed in a HDPE container

CAPETIZ 500 supplied in a bottle of 30 tablets packed in a HDPE container

MANUFACTURED & MARKETED BY:

Tizig Pharma Private Limited

Factory: Tukucha, Nala-1, Banepa, Nepal.

Regd. Office: Maligaun-5, Kathmandu, Nepal.

Capecitabine Dose Calculation According to Body Surface Area			
Dose level 255 mg/m^2/day		Number of tablets to be taken at each dose(morning and evening)	
Surface Area (m^2)	Total Dally *Dose (mg)	150 mg	500 mg
</=1.24	3000	3000	3
1.25-1.36	3300	3300	3
1.37-1.51	3600	3600	3
1.52-1.64	4000	4000	4
1.65-1.76	4300	4300	4
1.65-1.76	4600	4600	4
1.92-2.04	5000	5000	5
2.05-2.17	5300	5300	5
>/=2.18	5600	5600	5

Size: 100x182 mm