DRUG INTERACTIONS :
Antacid
The effect of an aluminum hydroxide- and magnesium hydroxide-containing antacid on the pharmacokinetics of was investigated in 12 cancer patients. There was a small increase in plasma concentrations of CAPECITABINE and one metabolite (5'-DFCR); there was no effect on the 3 major metabolites (S'-DFUR, 5-FU and FBAL).
Coumarin Anticoagulants
Altered coagulation parameters and/or bleeding have been reported in patients taking CAPECITABINE concomilantly with coumarin-dervivative anticoagulants such as warfarin and phenprocoumon. Patients taking coumarin-derivative anticoagulants concomitantly with CAPECITABINE should be monitored regularly for alterations in their coagulation parameters (PT or INR).
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.

ADVERSE REACTIONS :
Diarrhea, Nausea. Vomiting, Stomatitis, Abdominal pain, Constipation, Dyspepsia, Hand-and-Foot Syndrome, Dermatitis, Fatigue, Paraesthesia.
Shown below by body system are the adverse events in <5% of patients reported as related to the administration of CAPECITABINE and that were clinically at least remotely relevant. In parentheses is the incidence of grade 3 or 4 occurrences of each adverse event.
Gastrointestinal : intestinal obstruction (11), rectal bleeding (0.4), GI hemorrhage (0.2), esophagitis (0.4). gastritis, colitis, duodenitis, haematemesis, necrolizing enterocolitis.
Skin : increased sweating (0.2), photosensitivity (0.2), radiation recall syndrome (0.2).
General : chest pain (0.2)
Neurological : ataxia (0.4), encephalopathy (0.2), depressed level of consciousness (0.2), loss of consciousness (0.2).
Metabolism : cachexia (0.4) hypertriglyceridemia (0.2).
Respiratory : dyspnea (0.5), epistaxis (0.2) bronchospasm (0.2), respiratory distress (0.2).
Infections : oral candidiasis (0.2), upper respiratory tract infection (0.2), urinary tract infection (0.2), bronchitis (0.2), pneumonia (0.2), sepsis (0.4), bronchopneumonia (0.2), gastroenteritis (0.2), gastrointestinal candidiasis (0.2), laryngitis (0.2), esophageal candidiasis (0.2).
Musculoskeletal : bone pain (0.2), joint stiffness (0.2).
Cardiac : angina pectoris (0.2), cardiomyopathy (0.2).
Vascular : hypotension (0.2), hypertension (0.2), venous phlebitis and thrombophlebitis (0.2), deep venous thrombosis (0.7). lymphoedema (0.2), pulmonary embolism (0.4), cerebrovascular accident (0.2).
Blood : coagulation disorder (0.2), idiopathic thrombocytopenic purpura (0.2), pancytopenia (0.2).
Psychiatric : confusion (0.2).
Renal and Urinary : nocturia (0.2)
Hepatobiliary: hepatic fibrosis (0.2), cholestatic hepatitis (0.2), hepatitis (0.2).
Immune System: drug hypersentitivity (0.2).

OVERDOSE :
Medical management of overdose should include customary 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 S'-DFUR, a low-molecular weight metabolite of the parent compound.

STORAGE :
Store at a temperature not exceeding 30°C.

HOW SUPPLIED : A strip of 10 tablets.

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Unit No 209, Anandraj Industrial Estate 2nd Floor,
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B-1, Wagle Industrial Estate,Thane 400 604.
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D190119

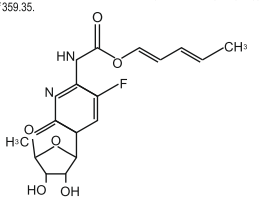
For the use of Registered Medical Practitioner Only

℞Capecitabine Tablets IP 500mg

HopeCap होपकेप

COMPOSITION :
Each film-coated tablet contains
CAPECITABINE IP 500 mg

DESCRIPTION :
CAPECITABINE 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 CAPECITABINE is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and has a molecular weight of 359.35.



CLINICAL PHARMACOLOGY :
CAPECITABINE is relatively noncytotoxic in vitro. This drug is enzymatically converted to fluorouracil (5-FU) in vivo.

BIOACTIVATION:
CAPECITABINE is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxyesterase 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'-DFUR to 5'-deoxy-5-fluorouridine.
(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.

MECHANISM OF ACTION:
Both normal and tumor cells metabolize 5-FU to f-fluoro-2-deoxyuridine monophosphate. (FdUMP) and 5-fluorouridine triphosphate (FUTP). These metabolites cause cell injury by two different mechanisms. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate from uracil. 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.

PHARMACOKINETICS :
Absorption : CAPECITABINE reached peak blood levels in about 1.5 hours (Tmax) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of CAPECITABINE with mean Cmax and AUCo-v decreased by 60% and 35%, respectively. The Cmax and AUC_{∞} 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
Distribution : Plasma protein binding of CAPECITABINE and its metabolites is less than 60%
Metabolism and Excretion : CAPECITABINE is extensively metabolized enzymatically 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 (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally b-ureido-propionase cleaves FUPA to a-fluoro-b-alanine (FBAL) which is cleared in the urine.

Special Populations
Age, Gender and Ethnicity : No formal studies were conduced to examine the effect of age or
gender or ethnicity on the pharmacokinetics of CAPECITABINE and its metabolites.
Hepatic Insufficiency : Both AUCo-∞ and Cmax of CAPECITABINE increased by 60% in patients with hepatic dysfunction compared to patients with normal hepatic function (n=14). The AUCo-∞ and Cmax of 5-FU was not affected. In patients with mild to moderate hepatic dysfunction due to liver metastases, caution should be exercised when CAPECITABINE is administered. The effect of severe hepatic dysfunction on CAPECITABINE is not known.
Renal Insufficiency : No formal pharmacokinetic study was conducted in patients with renal impairment.

INDICATIONS :
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, e.g., patients who have received.cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen.

DOSAGE AND ADMINISTRATION :
The recommended dose of CAPECITABINE is 2500 mg/m^2 administered orally daily with food for 2 weeks followed by a 1-week rest period given as 3-week cycles. The CAPECITABINE daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of the 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.

Dose level mg/m^2/day		Number of tablets to be taken 2500 at each dose (morning and evening)	
Surface Area (m^2)	Total Daily Dose (mg)	150mg	500mg
<1.24	3000	0	3
1.25-1.36	3300	1	3
1.37-1.51	3600	2	3
1.52-1.64	4000	0	4
1.65-1.76	4300	1	4
1.77-1.91	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 bycom 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 the dose has been reduced it should not be increased at a later time.

Recommended Dose Modifications*

Toxicity NCIC Grades'	During a Dose Adjustment Course of Therapy	for Next Cycle (% of starting dose)
* Grade 1	Maintain dose level	Maintain dose level
* Grade 2 -1st appearance	Interrupt unit resolved to grade 0-1	100%
-2nd appearance	Interrupt until resolved to grade 0-1	75%
-3rd appearance	Interrupt until resolved to grade 0-1	50%
-4th appearance	Discontinue Treatment permanently	
* Grades 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 -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	

* National Cancer Institute of Canada Common Toxicity Criteria was used except for the Hand-and-Foot Syndrome.
Dosage modifications are not recommended for grade 1 events. Therapy with CAPECITABINE should be interrupted upon the occurrence of a grade 2 or 3 adverse experience. Once the adverse event has solved or decreased in intensity to grade 1, then CAPECITABINE therapy may be restarted at full dose or as adjusted according to the above table. If a grade 4 experience occurs, therapy should be discontinued or interrupted until resolved or decreased to grade 1, and therapy should be restarted at 50% of the original dose. Doses of CAPECITABINE omitted for toxicity are not replaced or restored; instead the patient should resume the planned treatment cycles.
Adjustment of Starting Dose In Special Populations :
Hepatic Impairment: In patients 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 Impairment: Insufficient data are available in patients with renal impairment to provide a dosage recommendation.
Geriatrics: The elderly may be pharmacodynamically more sensitive to the toxic effects of 5-FU and therefore, physicians should exercise caution in monitoring the effects of CAPECITABINE in the elderly. Insufficient data are available to provide a dosage recommendation.

CONTRAINDICATIONS :CAPECITABINE is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil.

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. These events occurred within several days and up to several months after initiating CAPECITABINE therapy and, in a few cases, within one month after stopping CAPECITABINE. These events occurred in patients with and without liver metastasis. Patients taking coumarin-derivative anticoagulants concomitantly with CAPECITABINE should be monitored regularly for alterations in their coagulation parameters (PT or INR)
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.

PRECAUTIONS :
General :
Patients receiving therapy with CAPECITABINE should be monitored by a physician experienced in the use of cancer chemotherapeutic agents. 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 (palmarplantar erythrodysesthesia or chemotherapy induced acral erythema) is characterized by the following : numbness, dysesthesia/paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering, and severe pain. 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 and severe pain of the hands and/or feet and/or severe discomfort that causes the patient to be unable to work or perform activities of daily living. If grade 2 or 3 hand-and-foot syndrome occurs, administration of CAPECITABINE should be interrupted until the event resolves or decreases in intensity to grade 1.
Cardiac: There has been cardiotoxicity associated with fluorinated pyrimidine 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 metastasis should be carefully monitored when CAPECITABINE is administered. The effect of severe hepatic dysfunction on the disposition of CAPECITABINE is not known
Renal Insufficiency : There is little experience in patients with real impairment. Physicians should exercise caution when CAPECITABINE is administered
Drug-Food Interaction :
In all clinical trails, patients were instructed to administer CAPECITABINE within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that CAPECITABINE be administered with food.

Pregnancy : Category D
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 persons < 18 years of age have not been established.

PATIENT INFORMATION :
Patients and patients care givers should be informed of the expected adverse effects of CAPECITABINE, particularly nausea, vomiting, diarrhea and hand-and-foot syndrome and should be made aware that patient specific dose adaptations during therapy are expected and necessary. Patients should be encouraged to recognize the common grade 2 toxicities associated with CAPECITABINE treatment.
Diarrhea : Patients experiencing grade 2 diarrhea (an increase of 4 to 6 stools/day or nocturnal stools) or greater should be instructed to stop taking CAPECITABINE immediately. Standard antidiarrheal treatment (e.g.,loperamide) are recommended.
Nausea : Patients experiencing grade 2 nausea (food intake signficantly decreased but able to eat intermittently) or greater should be instructed to stop taking CAPECITABINE immediately. Initiation of symptomatic treatment is recommended.
Vomiting : Patients experiencing grade 2 vomiting (2 to 5 episodes in a 24-hour period) or later should be instructed to stop taking CAPECITABINE immediately. Initiation of symptomatic treatment is recommended.
Hand-and-Foot Syndrome : 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 should be instructed to stop taking CAPECITABINE immediately.
Stomatitis: Patients experiencing grade 2 stomatitis (Painful erythema, edema or ulcers of the mouth or tongue, but able to eat) or greater should be instructed to stop taking CAPECITABINE immediately. Initiation of symptomatic treatment is recommended.
Fever and Neutropenia : Patients who develop a fever of 100.5° F or greater or other evidence of potential infection should be instructed to call their physician.