*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 30ºC.

Marketed by:
NEOVA BIOGENE PRIVATE LIMITED
Monte Plaza, Malviya Marg,
Mulund (w), Mumbai-80, India

CAPESHILD 500 mg

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

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Capecitabine Tablets IP

COMPOSITION :

Each film coated tablet contains :

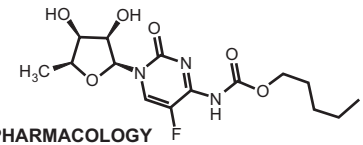
Capecitabine IP	500 mg.
Excipients	qs

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-[(penlyloxy) 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 pharmacokinentic of capecitabine and its metabolites have been evaluated in about 200 cancer patients over a dosage range cf 500 to 3500 mg/m^2/day. Over this range, the pharmacokinentic of capecitabine and its metabolite. 5'-DFCR were dose proportional and did not change over time. The increases in the AUC5 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 % of an hour. The inter-patient variability in the Cmax and Ai-JC of 5-FU was greater than 85%.

Following oral administration of 825 mg/m^2 capecitabine twice daily for 14 days, Japanese patients (n=18) had about 36% lower Cmax and 24% lower AUC for capecitabine than the Caucasian patients (n=22). Japanese patients had also about 25% lower Cmax and 34% lower AUC for HAL 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- fluorouracii.

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.

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 cardietoxidty associated with tiuorinatedpyilmidine therapy, including myocardial infarction, angina,dysrhythrnias, 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 dysfunctiondue 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 title experience in patients with renal impairment Physicians should exercise caution when Capecitabine is administered.

Hematologic: Capecitabine can lead neutiopenia, thrombocytopenia anddecreases 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 bemutagenic in vitro or in vivo.

Impairment of Fertility: Capecitabine causes a decrease in fertility bydisturbing 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 poi sons < 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

Coagulmathy: 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 entorecolitis 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 to avoid becoming pregnant while receiving treatment with Capedtabine.

DRUG INTERACTIONS

Antacid: Aluminum hydroxide- and magnesium hydroxide-containing antacid cause a small increase in elmsconcentration 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. 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-DFUR, a low-molecular weight metabolite of the parent compound.

DOSAGE AND ADMINISTRATION

The recommended dose of Capecitabine is 2500 mg/m2 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/m2/day Surface Area		Number of tablets to be taken at each dose (morning and evening)	
Surface Area (m2)	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 treatinent, dose interruptions and adjustment of Capecitabine dose. Once dose has been reduced it should not be increased at a later time

Recommended Dose Modifica ions		
Toxicity NCIC Grades	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 grace 0-1	100%
- 2° appearance		75%
-3. appearance	Interrupt until resolved fv 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 use except for the Hand-and-Foot Syndrome.