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

Capecitabine Tablets IP 500 mg

Capetaz ™

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Composition

Each film coated tablet contains:

Capecitabine IP 500mg

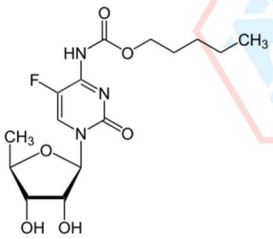
Excipients q.s

Colours: Red oxide of iron & Titanium Dioxide

DESCRIPTION

CAPETAZ 500 tablets containing Capecitabine 500mg are Peach colored capsule shaped film coaed tablets. 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. 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 pharmacokinetics of Capecitabine and its metabolites have been evaluated in about 200 cancer patients over a dosage range of 500 to 3500 mg/m2/day. Over this range, the pharmacokinetics of Capecitabine and did not change over time. The increases in the AUCs OF 5'-dfur and 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 34% lower AUC for capecitabine than the Caucasian patients. The clinical significance of these differences is unknown. No signigicant 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.

DOSAGE AND ADMINISTRATION

The recommended dose of Capecitabine is 2500 mg /m2 administered orally daily with food for 2weeks 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 225 mg/m2/day		Number of tablets to be taken at each dose (morning and evening)	
Surface Area (m2)	Total Daily* Dose (mg)	150 mg	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
1.65-1.76	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 NCCIC Grades*	During a Course of Therapy	Dose Adjustment for Next Cycle (% 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	Interrupt 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 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-Doot 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 tis 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 be pharmcodynamically 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.

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.

PRECAUTIONS

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

Hand-and-Foot Syndrome: Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy induced acral erythema) may 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 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 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, Mutagenesis & Impairment of Fertility

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 durgs 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.

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 Capecitabine with food, it is recommended that Capecitabine be administered with food.

ADVERSE REACTIONS

Adverse effects 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

Hepatobilliary: Hyperbilirubinemia

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 coumarinderivative anticoagulants concomitantly with Capecitabine should be monitored regularly for alterations in their coagulation parameters.

Phenytoin: 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.

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 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.

CONTRAINDICATIONS

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

STORAGE

Store in a cool, dry place. Protect from light.

SHELF LIFE: 24months

PRESENTATION: 10 Strip of 10 Tablets.

HOW SUPPLIED

Capetaz ™ 500MG

Capecitabine Tablets IP 500mg

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
www.zuviuslifesciences.in