165mm

82.5mm

82.5mm

155mm

studies, this dose in mice produced 5'-DFUR AUC values about 0.7 times the corresponding values in patients administered the recommended daily dose.

Pediatric Use:
The safety and effectiveness of CAPECITA in persons <18years of age have not been established.

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 CAPECITA therapy.

DRUG INTERACTIONS
Drugs Metabolized by Cytochrome P450 Enzymes: In vitro enzymatic studies with human liver microsomes indicated that capecitabine and its metabolites had no inhibitory effects on substrates of cytochromeP450 for the major iso enzymes such as 1A2,2A6, 3A4,2C9,2C19, 2D6, and 2E1, suggesting a low likelihood of interactions with drugs metabolized by cytochrome P450 enzymes.

Antacid:
When Maalox (20mL), an aluminum hydroxide- and magnesium hydroxide containing antacid, was administered immediately after capecitabine (1250 mg/m2, n=12 cancer patients), AUC and Cmax increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%, respectively, for 5'- DFCR. No effect was observed on the other three major metabolites (5-DFUR, 5-FU, FBAL) of capecitabine.
CAPECITA has a low potential for pharmacokinetic interactions related to plasma protein binding.

OVERDOSAGE
Acute: Based on experience in animals and in humans treated up to doses of 3514 mg/m2/day, the anticipated manifestations of acute overdose would be nausea, vomiting, diarrhea, gastrointestinal irritation and bleeding, and bone marrow depression. 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 5'-DFUR, a low molecular weight metabolite of the parent compound.

PRESENTATION
Capecita 500mg Tablet available in blister pack of 12 x10's & 1 x10's

Dosage:
As directed by the physician.

INSTRUCTIONS:
Store at 25°C, (Excursions permitted between 15°C to 30°C).
Protect from sunlight & moisture.
Keep out of the reach of children.
To be dispensed on the prescription of a registered medical practitioner only.

خوراک : ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات : دوا کو ۲۵ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔
(درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے)۔
دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

Kaizen Pharmaceuticals (Pvt.) Ltd.

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Capecita

(Capecitabine)

500mg Tablets

کیپیسیٹا

(کیپیسیٹابائن)

۵۰۰ ملی گرام گولیاں

COMPOSITION:
Each film coated tablet contains:
Capecitabine..... 500mg

WARNING: CAPECITA -WARFARIN INTERACTION

Patients receiving concomitant Capecita and oral coumarin-derivative anticoagulants such as warfarin and phenprocoumon should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. Altered coagulation parameters and/or bleeding, including death, have been reported during concomitant use.

- Occurrence: Within several days and up to several months after initiating Capecita therapy; may also be seen within 1 month after stopping Capecita
- Predisposing factors: age>60 and diagnosis of cancer

CLINICAL PHARMACOLOGY
DESCRIPTION
CAPECITA (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. Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26mg/mL at 20°C.

PHARMACODYNAMICS
Mechanism Of Action
Both normal and tumor cells metabolize 5-FU to 5-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, N5-10methylenetetrahydrofolate, 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. This metabolic error can interfere with RNA processing and protein synthesis.

PHARMACOKINETICS
Capecitabine reached peak blood levels in about 1.5 hours (Tmax) with peak 5-FU levels occurring Slightly later, at 2hours.Food reduced both the rate and extent of absorption of capecitabine with mean Cmax and AUC0- ∞ decreased by 60% and 35%, respectively. The Cmax and AUC0- ∞ 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. Plasma protein binding of capecitabine and its metabolites is less than 60% and is not concentration- dependent. Capecitabine was primarily bound to human albumin (approximately 35%). 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 (FUH2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5- fluoro-ureido-propionic acid (FUPA). Finally, β-ureido-propionase cleaves FUPA to α-fluoro- β– alanine (FBAL) which is cleared in the urine.
Capecitabine and its metabolites are predominantly excreted in urine; 95.5% of administered capecitabine dose is recovered in urine. Fecal excretion is minimal (2.6%). The major metabolite excreted in urine is FBAL which represents57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.

165mm

82.5mm

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SPECIAL POPULATION

Age, Gender and Ethnicity: No formal studies we reconducted to examine the effect of age or gender or ethnicity on the pharmacokinetics of capecitabine and its metabolites.
Hepatic Insufficiency: CAPECITA has been evaluated in 13 patients with mild to moderate hepatic dysfunction due to liver metastases defined by a composite score including bilirubin, AST/ALT and alkaline phosphatase following a single 1255 mg/m2 dose of capecitabine. Both AUC0- ∞ and Cmax of capecitabine increased by 60% in patients with hepatic dysfunction compared to patients with normal hepatic function (n=14). The AUC0-∞ 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 CAPECITA is administered. The effect of severe hepatic dysfunction on CAPECITA is not known.

THERAPEUTIC INDICATIONS

CAPECITA 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 anthracydine therapy is not indicated, e.g., patients who have received cumulative doses of 400 mg/m2 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 ananthracydine containing adjuvant regimen. It is also used in colorectal cancer.

DOSAGE & ADMINISTRATION

The recommended dose of CAPECITA is 1250 mg/m2 administered orally twice daily (morning and evening; equivalent to 2500 mg/m2 total daily dose) administered orally daily with food for 2 weeks followed by a 1-week rest period given as 3-week cycles. The CAPECITA daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. CAPECITA 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 1250 mg/m^2 Twice a Day		Number of Tablets to be Taken at Each Dose (Morning and Evening)	
Surface Area (m^2)	Total Daily Dose* (mg)	150 mg	500 mg
≤ 1.25	3000	0	3
1.26-1.37	3300	1	3
1.38-1.51	3600	2	3
1.52-1.65	4000	0	4
1.66-1.77	4300	1	4
1.78-1.91	4600	2	4
1.92-2.05	5000	0	5
2.06-2.17	5300	1	5
≥ 2.18	5600	2	5

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

METHOD OF ADMINISTRATION

For oral administration only.

ADVERSE REACTIONS

Most common adverse reactions (⊠30%) were:
- Diarrhea
- hand-and-foot syndrome
- nausea, vomiting
- abdominal pain
- fatigue/weakness
- hyperbilirubinemia.

CONTRAINDICATIONS

CAPECITA is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil. CAPECITA is also contraindicated in patients with severe renal impairment (creatinine clearance below 30mL/min [Cockroft and Gault])

PRECAUTIONS

General:
Patients receiving therapy with CAPECITA 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 (palmar-plantar 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 grade2 or 3 hand-and- foot syndrome occurs, administration of CAPECITA should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of CAPECITA should be decreased.

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 metastases should be carefully monitored when CAPECITA is administered. The effect of severe hepatic dysfunction on the disposition of CAPECITA is not known.

Hyperbilirubinemia:
Grade3 or 4 hyperbilirubinemia occurred in 17%(n=97) of 570 patients with either metastatic breast or colorectal cancer who received a dose of 2510 mg/m2 daily for 2 weeks followed by a 1- week rest period. Of 339 patients who had hepatic metastases at baseline and 231 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 21.2% and 10.4%, respectively. Seventy-four (76%) of the 97 patients with grade 3 or 4 hyperbilirubinemia also had concurrent elevations in alkaline phosphatase and/or hepatic transaminases;6%of these were grade 3 or 4. Only 4 patients (4%) had elevated hepatic transaminases without a concurrent elevation in alkaline phosphatase. If drug related grade 2-4 elevations in bilirubin occur, administration of CAPECITA should be immediately interrupted until the hyperbilirubinemia resolves or decreases in intensity to grade 1. NCIC grade 2 hyperbilirubinemia is defined as 1.5 x normal, grade 3 hyperbiliru-binemia as 1.5-3 x normal and grade 4hyperbilirubinemiaas>3 x normal.

Hematologic:
In 570 patients with either metastatic breast or colorectal cancer who received a dose of 2510 mg/m2 administered daily for 2 weeks followed by a1-week rest period, 4%, 2%, and 3%of patients hadgrade3 or4 neutropenia, thrombocytopenia and decreases in hemoglobin, respectively.

Carcinogenesis, Mutagenesis and Impairment of Fertility:
Long-term studies in animals to evaluate the carcinogenic potential of capecitabine have not been conducted. Capecitabine was not mutagenic in vitro to bacteria (Ames test) or mammalian cells (Chinese hamster V79/HPRT gene mutation assay). Capecitabine was dastogenic in vitro to human peripheral blood lymphocytes but not dastogenic in vivo to mouse bone marrow (micronucleus test). Fluorouracil causes mutations in bacteria and yeast. Fluorouracil also causes chromosomal Abnormalities in the mouse micronucleus test in vivo.

Impairment of Fertility:
In studies of fertility and general reproductive performance in mice, oral capecitabine doses of 760 mg/kg/day disturbed estrus and consequently caused a decrease in fertility. In mice that became pregnant, no fetuses survived this dose. The disturbance in estrus was reversible. In males, this dose caused degenerative changes in the testes, including decreases in the number of spermatocytes and spermatids. In separate pharmacokinetic