141.0 mm

206.0 mm

CAPCITA 500mg Tablet

(Capecitabine)

کیپسیٹا ۵۰۰ ملی گرام ٹیبلٹ

(کیپسیٹابین)

COMPOSITION:
Each film coated tablet contains:
Capecitabine 500mg
(USP Specifications)
DESCRIPTION:
CAPCITA (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 26 mg/mL at 20ºC.
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
CLINICAL PHARMACOLOGY:
Capecitabine is relatively non-cytotoxic in vitro. This drug is enzymatically converted to 5- fluorouracil (5-FU) in vivo. 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'-DFCR 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 higherconcentrations than surrounding normal tissues.
PHARMACOKINETICS:
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 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 represents 57% of the administered dose. About 3% of the administered dose is excreted in urine as unchanged drug.
Special Populations:
Age, Gender and Ethnicity: No formal studies were conducted to examine the effect of age or gender or ethnicity on the pharmacokinetics of capecitabine and its metabolites.
Hepatic Insufficiency: CAPCITA 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 CAPCITA is administered. The effect of severe hepatic dysfunction on CAPCITA is not known.
Drug-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 cytochrome P450 for the major isoenzymes 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.
CAPCITA has a low potential for pharmacokinetic interactions related to plasma protein binding.
INDICATIONS AND USAGE:
CAPCITA 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, eg, 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 an anthracycline containing adjuvant regimen. It is also used in colorectal cancer.
CONTRAINDICATIONS:
CAPCITA is contraindicated in patients who have a known hypersensitivity to 5-fluorouracil.
CAPCITA is also contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).
WARNINGS
Renal Insufficiency:
In patients with moderate renal impairment (creatinine clearance 30-50 mL/min [Cockroft and Gault]) at baseline, a dose reduction to 75% of the CAPCITA starting dose is recommended. In patients with mild renal impairment (creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. . Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event with subsequent dose adjustments.
Coagulopathy:
Altered coagulation parameters and/or bleeding have been reported in patients taking CAPCITA concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating CAPCITA therapy and, in a few cases, within one month after stopping CAPCITA. These events occurred in patients with and without liver metastases. Patients taking coumarin derivative anticoagulants concomitantly with CAPCITA should be monitored regularly for alterations in their coagulation parameters (PT or INR.)
Diarrhea:
CAPCITA can induce diarrhea, sometimes severe. Patients with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. The median time to first occurrence of grade 2-4 diarrhea was 31 days (range from 1 to 322 days). National Cancer Institute of Canada (NCIC) grade 2 diarrhea is defined as an increase of 4 to 6 stools/day or nocturnal stools, grade 3 diarrhea as an increase of 7 to 9 stools/day or incontinence and malabsorption, and grade 4 diarrhea as an increase of ≥10 stools/day or grossly bloody diarrhea or the need for parenteral support. If grade 2, 3 or 4 diarrhea occurs, administration of CAPCITA should be immediately interrupted until the diarrhea resolves or decreases in intensity to grade 1. Following grade 3 or 4 diarrhea, subsequent doses of CAPCITA should be decreased .Standard antidiarrheal treatments (eg, loperamide) are recommended.
Necrotizing enter colitis (typhlitis) has been reported.
Geriatric Patients (gastrointestinal toxicity):
Patients ≥80 years old may experience a greater incidence of gastrointestinal grade 3 or 4 adverse events. Among the 14 patients 80 years of age and greater treated with capecitabine, three (21.4%), three (21.4%) and one (7.1%) patients experienced reversible grade 3 or 4 diarrhea, nausea and vomiting, respectively.
Among the 313 patients age 60 to 79 years old, the incidence of gastrointestinal toxicity was similar to that in the overall population.
Pregnancy:
CAPCITA may cause fetal harm when given to a pregnant woman. Capecitabine at doses of 198 mg/kg/day during organogenesis caused teratogenic malformations and embryo death in mice. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.2 times the corresponding values in patients administered the recommended daily dose. Teratogenic malformations in mice included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilation of cerebral ventricles. At doses of 90 mg/kg/day, capecitabine given to pregnant monkeys during organogenesis caused fetal death. This dose produced 5'-DFUR AUC values about 0.6 times the corresponding values in patients administered the recommended daily dose. There are no adequate and well-controlled studies in pregnant women using CAPCITA. 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 CAPCITA.
PRECAUTIONS
General:
Patients receiving therapy with CAPCITA 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 grade 2 or 3 hand-and-foot syndrome occurs, administration of CAPCITA should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of CAPCITA 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 **CAPCITA** is administered. The effect of severe hepatic dysfunction on the disposition of **CAPCITA** is not known.
Hyperbilirubinemia:
Grade 3 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 CAPCITA 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 hyperbilirubinemia as 1.5-3 x normal and grade 4 hyperbilirubinemia as >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 a 1-week rest period, 4%, 2%, and 3% of patients had grade 3 or 4 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 clastogenic in vitro to human peripheral blood lymphocytes but not clastogenic 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 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 **CAPCITA** in persons <18 years 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 CAPCITA therapy.

ADVERSE REACTIONS:
The following table shows the adverse events occurring in ≥5% of patients reported as at least remotely related to the administration of CAPCITA. Rates are rounded to the nearest whole number. The data are shown both for the study in stage IV breast cancer and for a group of 570 patients with breast and colorectal cancer who received a dose of 2510 mg/m2 administered daily for 2 weeks followed by a 1-week rest period. The 570 patients were enrolled in 6 clinical trials (162 from the breast cancer trial described under CLINICAL STUDIES, 83 other patients with breast cancer and 325 patients with colorectal cancer). The mean duration of treatment was 121 days. A total of 71 patients (13%) discontinued treatment because of adverse events/intercurrent illness.

Percent Incidence of Adverse Events Considered Remotely, Possibly or Probably Related to Treatment in ≥ 5% of Patients.

Adverse Event	Phase 2 Trial in Stage IV Breast Cancer (n=162)			Overall Safety Database (n=570)		
Body System/Adverse Event	**Total**	**Grade 3**	**Grade 4**	**Total**	**Grade3**	**Grade 4**
GI						
Diarrhea	57	12	3	5	11	2
Nausea	53	4	-	44	4	-
Vomiting	37	4	-	26	3	-
Stomatitis	24	7	-	23	4	-
Abdominal pain	20	4	-	17	4	-
Constipation	15	1	-	9	1	-
Dyspepsia	8	-	-	6	-	-
Skin and Subcutaneous				-		-
Hand-and-Foot Syndrome	57	11	-	45	13	-
Dermatitis	57	1	-	31	1	-
Nail disorder	1	-	-	4	-	-
General						
Fatigue	41	8		34	5	
Pyrexia	12	1		10		
Pain in limb	6	1		4		
Neurological						
Paraesthesia	21	1		12		
Headache	9	1		7	1	
Dizziness	8	-		5		
Insomnia	8	-		3		
Metabolism						
Anorexia	23	3		20	2	1
Dehydration	7	4	1	5	2	
Eye						
Eye irritation	15	-		10		
Musculoskeletal						
Myalgia	9	-				
Cardiac				4		
Edema	9	1				
Blood				6		
Neutropenia	26	2	2	22	3	2
Thrombocytopenia	24	3	1	21	1	1
Anemia	72	3	1	74	2	10
Lymphopenia	94	44	15	94	36	4
Hepatobiliary						
Hyperbilirubinemia	22	9	2	34	14	3

Shown below by body system are the adverse events in <5% of patients reported as related to the administration of CAPCITA 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 (1.1), rectal bleeding (0.4), GI hemorrhage (0.2), esophagitis (0.4), gastritis, colitis, duodenitis, haematemesis, necrotizing 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
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 hypersensitivity (0.2).

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.

DOSAGE AND ADMINISTRATION:
The recommended dose of CAPCITA 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 CAPCITA daily dose is given orally in two divided doses (approximately 12 hours apart) at the end of a meal. CAPCITA 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.

CAPCITA Dose Calculation According to Body Surface Area

Dose level 2500 mg/m^2/day		Number of tablets to be taken at eacl dose (morning and evening)	
Surface Area (m^2)	**Total Daily* Dose (mg)**	**150 mg**	**500 mg**
≤ 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 by 2 to allow equal morning and evening doses.

Dose Modification Guidelines: Patients should be carefully monitored for toxicity. Toxicity due to CAPCITA administration may be managed by symptomatic treatment, dose interruptions and adjustment of CAPCITA dose. Once the dose has been reduced it should not be increased at a later time. The phenytoin dose may need to be reduced when phenytoin is concomitantly administered with **CAPCITA.**

Recommended Dose Modifications

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*		
-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	
Toxicity NCIC Grades*	**During a Course of Therapy**	**Dose Adjustment for Next Cycle (% of starting dose**
• *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-Foot Syndrome.

Dosage modifications are not recommended for grade 1 events. Therapy with CAPCITA should be interrupted upon the occurrence of a grade 2 or 3 adverse experience. Once the adverse event has resolved or decreased in intensity to grade 1, then CAPCITA 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: In patients with moderate renal impairment (creatinine clearance 30-50 mL/min [Cockroft and Gault, as shown below]) at baseline, a dose reduction to 75% of the CAPCITA starting dose (from 2500 mg/m^2/day to 1900 mg/m^2/day) is recommended. In patients with mild renal impairment (creatinine clearance 51-80 mL/min) no adjustment in starting dose is recommended. Careful monitoring and prompt treatment interruption is recommended if the patient develops a grade 2, 3, or 4 adverse event with subsequent dose adjustments as outlined in the table above. CAPCITA is contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min [Cockroft and Gault]).
Cockroft and Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{Age[yrs]})\ (\text{Bodywt [kg]})}{(72)\ (\text{Serum creatinine [mg/dL]})}$$

Creatinine clearance for females = 0.85 x male value

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 CAPCITA in the elderly. Insufficient data are available to provide a dosage recommendation.
Storage & Instructions:
Store between 15-25°C. Protect from sunlight, heat and moisture. Keep out of the reach of children. Use as directed by the oncologist.
To be sold on the prescription of a registered oncologist or on demand from cancer hospitals, institutions and oncologists only.

HOW SUPPLIED
CAPCITA 500mg Tablet:
120 film coated tablets.

خوراک وطریقہ استعمال:
سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات:
۱۵-۲۵ ڈگری سینٹی گریڈ کے درمیان رکھیں۔
دھوپ، گرمی اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخے پر فروخت کریں۔

Manufactured by:
PHARMASOL
PRIVATE LIMITED
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.