

# Cabita

Capecitabine 500 mg Tablet

**COMPOSITION:** Each film coated tablet contains Capecitabine USP 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. Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/ml at 20°C.

**CLINICAL PHARMACOLOGY:** Capecitabine is relatively non-cytotoxic in vitro. This drug is enzymatically converted to 5-fluorouracil (5-FU) in vivo. 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, N<sup>5</sup>-10-methylenetetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidine from 2'-deoxyuridylate. 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:

**Absorption, Distribution, Metabolism and Excretion:** Capecitabine reached peak blood levels in about 1.5 hours (T<sub>max</sub>) with peak 5-FU levels occurring slightly later, at 2 hours. Food reduced both the rate and extent of absorption of Capecitabine with mean C<sub>max</sub> and AUC<sub>0-∞</sub> decreased by 60% and 30% respectively. The C<sub>max</sub> and AUC<sub>0-∞</sub> of 5-FU were also reduced by food by 43% and 21% respectively. Food delayed T<sub>max</sub> 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-urido-propionic acid (FUPA). Finally, β-ureid-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.

#### INDICATIONS

**Colorectal Cancer:** Capecitabine is indicated as a single agent for adjuvant treatment in patients with Dukes' C colon cancer who have undergone complete resection of the primary tumor when treatment with fluoropyrimidine therapy alone is preferred. Capecitabine was non-inferior to 5-fluorouracil and Calcium folinate for disease-free survival (DFS). Although neither Capecitabine nor combination chemotherapy prolongs overall survival (OS), combination chemotherapy has been demonstrated to improve disease-free survival compared to 5-fluorouracil or Calcium folinate.

Capecitabine is indicated as first-line treatment of patients with metastatic colorectal carcinoma when treatment with fluoropyrimidine therapy alone is preferred. Combination chemotherapy has shown a survival benefit compared to 5-fluorouracil or Calcium folinate alone. A survival benefit over 5-fluorouracil or Calcium folinate has not been demonstrated with Capecitabine monotherapy. Use of Capecitabine instead of 5-fluorouracil or Calcium folinate in combinations has not been adequately studied to assure safety or preservation of the survival advantage.

**Breast Cancer:** Capecitabine in combination with Docetaxel is indicated for the treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing chemotherapy. Capecitabine monotherapy is also 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 400mg/m<sup>2</sup> 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 Cabita is 1250 mg/m<sup>2</sup> administered orally twice daily (morning and evening; equivalent to 2500 mg/m<sup>2</sup> total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles. Cabita tablets should be swallowed with water within 30 minutes after a meal. In combination with Docetaxel, the recommended dose of Cabita is 1250 mg/m<sup>2</sup> twice daily for 2 weeks followed by a 1-week rest period, combined with Docetaxel at 75mg/m<sup>2</sup> as a 1-hour intravenous infusion every 3 weeks. Pre-medication, according to the Docetaxel labeling, should be started prior to Docetaxel administration for patients receiving the Cabita plus Docetaxel combination.

Adjuvant treatment in patients with Dukes' C colon cancer is recommended for a total of 6 months, ie, Cabita 1250 mg/m<sup>2</sup> orally twice daily for 2 week followed by a 1-week rest period, given as 3-week cycles for a total of 8 cycles (24 weeks). Or, as directed by the registered physicians.

**SIDE EFFECTS:** The most common side effects are: hand-and-foot syndrome, diarrhea, nausea, vomiting, sores in the mouth and throat (stomatitis), stomach area pain (abdominal pain), upset stomach, constipation, loss of appetite, and too much water loss from the body (dehydration) (These side effects are more common in patients age 80 and older). Other common side effects are rash; dry, itchy or discolored skin; nail problems; hair loss; tiredness; weakness; dizziness; headache; fever; pain (including chest, back, joint and muscle pain); trouble sleeping; and taste problems.

**CONTRAINDICATIONS:** Capecitabine is contraindicated in patients with known hypersensitivity to Capecitabine or to any of its components. Capecitabine is contraindicated in patients who have a history of severe renal impairment & known hypersensitivity to fluorouracil.

**DRUG INTERACTIONS:** If certain medications are combined, there is a possibility for negative drug interactions. When Capecitabine is taken with Calcium folinate or phenytoin, for example, it can alter the levels of medication in your blood and can increase your risk of side effects. When Warfarin and Capecitabine are taken together, there is an increased risk of bleeding.

**PRECAUTIONS:** Patients treated with Capecitabine should be carefully monitored for toxicity. Most adverse events are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced. The spectrum of cardiotoxicity observed with Capecitabine is similar to that of other fluorinated pyrimidines.

**Use in Pregnancy & Lactation:** This medicine should not be used during pregnancy as it may be harmful to the unborn baby. Women who could get pregnant should use effective contraception to prevent pregnancy, and men should use effective contraception to prevent fathering a child, both during treatment, and for at least a few months after treatment is finished.

**Lactation:** It is not known if this medicine passes into breast milk. Mothers who need to take this medicine should not breastfeed.

**OVERDOSE:** The manifestations of acute overdose would include 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 using dialysis as a treatment for Capecitabine overdose has been reported, dialysis may be of benefit in reducing circulating concentrations of 5'-DFUR, a low-molecular-weight metabolite of the parent compound.

**Storage:** Store below 25°C in a dry place. Keep the medicine out of reach of children.

**Packing:** Each box contains 28 tablets in Alu-Alu blister pack.



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