Capcitab®

Capecitabine Ph. Eur. Film Coated Tablet

DESCRIPTION

Capcitab® is a preparation of Capecitabine. Enzymes convert Capecitabine 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^{5-10}-methylene tetrahydrofolate, bind to thymidylate synthase (TS) to form a covalently bound ternary complex. This binding inhibits the formation of thymidylate 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: Following oral administration of 1255 mg/m^2 BID to cancer patients, Capecitabine reached peak blood levels in about 1.5 hours (T_{max}) 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_{max} and $AUC0_{0-\infty}$ decreased by 60% and 35%, respectively. The C_{max} and $AUC_{0-\infty}$ of 5-FU were also reduced by food by 43% and 21%, respectively. Food delayed T_{max} of both parent and 5-FU by 1.5 hours.

Distribution: 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 has a low potential for pharmacokinetic interactions related to plasma protein binding.

Metabolism: 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 (FUH 2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-ureido-propionic acid (FUPA). Finally,β-ureido-propionase cleaves FUPA to α-fluoro-β-alanin(FBAL) which is cleared in the urine.

Excretion: 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. The elimination half-life of both parent Capecitabine and 5-FU was about 0.75 hour.

INDICATIONS

- Adjuvant Colon Cancer: Patients with Dukes' C colon cancer
- Metastatic Colorectal Cancer: First-line as monotherapy when treatment with Fluoropyrimidine therapy alone is preferred
- Metastatic Breast Cancer:
  - » In combination with Docetaxel after failure of prior anthracycline - containing therapy
  - » As monotherapy in patients resistant to both paclitaxel and an anthracycline-containing regimen

DOSAGE AND ADMINISTRATION

- Take **Capcitab®** with water within 30 minutes after a meal.
- Monotherapy: 1250 mg/m^2 twice daily orally for 2 weeks followed by a one week rest period in 3-week cycles.
- Adjuvant treatment is recommended for a total of 6 months (8 cycles).
- In combination with Docetaxel, the recommended dose of Capecitabine is 1250 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period, combined with Docetaxel at 75 mg/m^2 as a 1-hour IV infusion every 3 weeks.
- **Capcitab®** dosage may need to be individualized to optimize patient management.
- Reduce the dose of **Capcitab®** by 25% in patients with moderate renal impairment.

CONTRAINDICATIONS

- Severe Renal Impairment
- Hypersensitivity

SIDE EFFECTS

- Diarrhea, nausea, vomiting, abdominal pain
- Hand-and-foot syndrome
- Fatigue/weakness
- Hyperbilirubinemia

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.

WARNINGS AND PRECAUTIONS

- **Coagulopathy:** May result in bleeding, death. Monitor anticoagulant response (e.g., INR) and adjust anticoagulant dose accordingly.
- **Diarrhea:** May be severe. Interrupt Capecitabine treatment immediately until diarrhea resolves or decreases to grade 1. Recommend standard antidiarrheal treatments.
- **Cardiotoxicity:** Common in patients with a prior history of coronary artery disease.
- **Dehydration and Renal Failure:** Interrupt Capecitabine treatment until dehydration is corrected. Potential risk of acute renal failure secondary to dehydration. Monitor and correct dehydration.
- **Increased Risk of Severe or Fatal Adverse Reactions in Patients with Low or Absent Dihydropyrimidine Dehydrogenase (DPD) Activity:** Withhold or permanently discontinue Capecitabine in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No Capecitabine dose has been proven safe in patients with absent DPD activity.
- **Pregnancy:** Can cause fetal harm. Advise women of the potential risk to the fetus.
- **Mucocutaneous and Dermatologic Toxicity:** Severe mucocutaneous reactions, Steven-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), have been reported. Capecitabine should be permanently discontinued in patients who experience a severe mucocutaneous reaction during treatment. Capecitabine may induce hand-and-foot syndrome. Interrupt Capecitabine treatment until the hand-and-foot syndrome event resolves or decreases in intensity.
- **Hyperbilirubinemia:** Interrupt Capecitabine treatment immediately until the hyperbilirubinemia resolves or decreases in intensity.
- **Hematologic:** Do not treat patients with neutrophil counts <1.5 x 10^9/L or thrombocyte counts <100 x 10^9/L. If grade 3-4 neutropenia or thrombocytopenia occurs, stop therapy until condition resolves.

DRUG INTERACTIONS

- **Anticoagulants:** Monitor anticoagulant response (INR or prothrombin time) frequently in order to adjust the anticoagulant dose as needed.
- **Phenytoin:** Monitor phenytoin levels in patients taking Capecitabine concomitantly with phenytoin. The phenytoin dose may need to be reduced.
- **Leucovorin:** The concentration of 5-Fluorouracil is increased and its toxicity may be enhanced by leucovorin.
- **CYP2C9 substrates:** Care should be exercised when Capecitabine is co-administered with CYP2C9 substrates.
- Food reduced both the rate and extent of absorption of Capecitabine.

USE IN PREGNANCY AND LACTATION

Pregnancy Category D. There are no adequate and well controlled studies of Capecitabine in pregnant women. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving Capecitabine, the patient should be apprised of the potential hazard to the fetus. Women should be advised to avoid becoming pregnant while receiving treatment with Capecitabine.

It is not known whether this 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 from Capecitabine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

PHARMACEUTICAL PRECAUTION

Storage Condition

Store below 30 °C temperature. Keep away from light and wet place. Keep out of reach of children.

PACKAGING

Capcitab® 500 Tablet: Box containing 7 strips of 4 tablets each. Each film coated tablet contains Capecitabine Ph. Eur. 500 mg.

SK+F ONCOLOGY

Manufactured by
ESKAYEF PHARMACEUTICALS LIMITED
RUPGANJ, NARAYANGANJ, BANGLADESH
® REGD. TRADEMARK
R/PM0518 V05