Xitabin

Capecitabine USP

COMPOSITION

Xitabin Tablet: Each film coated tablet contains Capecitabine USP 500 mg.

Xitabin 150 Tablet: Each film coated tablet contains Capecitabine USP 150 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.

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, N^{5-10}-methylenetetrahydrofolate, 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.

Pharmacodynamics/Kinetics:

Absorption, Distribution, Metabolism and Excretion

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 AUC_{0-a} decreased by 60% and 35% respectively. The C_{max} and AUC_{0-a} 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.

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 (FUH_2). Dihydropyrimidinase cleaves the pyrimidine ring to yield 5-fluoro-urido-propionic acid (FUPA). Finally, b-ureid-propionase lceaves FUPA to a-fluoro-b 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.

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. Physicians should consider these results when prescribing single-agent Capecitabine in the adjuvant treatment of Dukes' colon cancer.

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 400 mg/m^2 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.

HER2-overexpressing metastatic breast cancer

Indicated in combination with capecitabine for treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

Early stage HER2-negetive breast cancer

Patients with early-stage HER2-negative breast cancer with pathologic invasive residual disease at surgery following standard anthracycline- and taxane-based preoperative therapy may be offered up to six to eight cycles of adjuvant capecitabine.

Use in Pregnancy

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.

Use in Lactation

It is not known if this medicine passes into breast milk. Mothers who need to take this medicine should not breastfeed. Seek medical advice from your doctor.

DOSAGE AND ADMINISTRATION

The recommended dose of Xitabin is 1250 mg/m² administered orally twice daily (morning and evening; equivalent to 2500 mg/m² total daily dose) for 2 weeks followed by a 1-week rest period given as 3-week cycles. Xitabin tablets should be swallowed with water within 30 minutes after a meal.

In combination with docetaxel, the recommended dose of Xitabin is 1250 mg/m² twice daily for 2 weeks followed by a 1-week rest period, combined with docetaxel at 75 mg/m² 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 Xitabin plus docetaxel combination.

Adjuvant treatment in patients with Dukes' C colon cancer is recommended for a total of 6 months, ie, Xitabin 1250 mg/m² orally twice daily for 2 weeks followed by a 1-week rest period, given as 3-week cycles for a total of 8 cycles (24 weeks).

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 and unexpected reactions to fluoropyrimidine therapy or with known hypersensitivity to fluorouracil.

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.

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. Single doses of Capecitabine were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg (2.4, 4.8, and 9.6 times the recommended human daily dose on a mg/m²basis).

ADVERSE EFFECTS

The most common side effects of Capecitabine 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. Tell your doctor if you have heart problems because you could have more side effects related to your heart.

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.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store below 30°C, dry place and away from light. Keep out of the reach of children.

Presentation and Packaging

Xitabin Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

Xitabin 150 Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.

Manufactured By
BEACON® Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

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