

For the use of a Registered Medical Practitioner or a Hospital only

Rx Capecitabine Tablets USP 500 mg

ReliCitabine™ 500

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.

COMPOSITION

ReliCitabine is supplied as film-coated tablets for oral administration containing 500 mg capecitabine.

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 tumour when treatment with fluoropyrimidine therapy alone is preferred.
- 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-FU/LV alone.

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/m² of doxorubicin or doxorubicin equivalents.

DOSAGE AND ADMINISTRATION

The recommended dose of Capecitabine 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. Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

In combination with docetaxel, the recommended dose of Capecitabine 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 Capecitabine plus docetaxel combination. Table 1 displays the total daily dose by body surface area and the number of tablets to be taken at each dose. Adjuvant treatment in patients with Dukes' C colon cancer is recommended for a total of 6 months, ie, Capecitabine 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).

Table 1 : Capecitabine Dose Calculation According to Body Surface Area

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)
	500 mg
1.25	3000
1.26-1.37	3300
1.38-1.51	3600
1.52-1.65	4000
1.66-1.77	4300
1.78-1.91	4600
1.92-2.05	5000
2.06-2.17	5300
2.18	5600

*Total Daily Dose divided by 2 to allow equal morning and evening doses
Dose modification for the use of Capecitabine as monotherapy is shown in table 2.

Table 2: Recommended Dose Modifications With Capecitabine Monotherapy

Toxicity NCIC Grades*	During a Course of Therapy	Dose Adjustment for Next Treatment (% 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	
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 Capecitabine should be interrupted upon the occurrence of a grade 2 or 3 adverse experience.

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 carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'-DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumours, 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 higher concentrations than surrounding normal tissues.

Mechanism of Action

Both normal and tumour 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 co-factor, N⁵,N¹⁰-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.

Human Pharmacokinetics

The pharmacokinetics of Capecitabine and its metabolite, 5'-DFCR were dose proportional and did not change over time. The increases in the AUCs of 5'-DFUR and 5-FU, however, were greater than proportional to the increase in dose and the AUC of 5-FU was 34% higher on day 14 than on day 1. The elimination half-life of both parent capecitabine and 5-FU was about ¾ of an hour. The inter-patient variability in the C_{max} and AUC of 5-FU was greater than 85%.

Capecitabine reached peak blood levels in about 1.5 hours (T_{max}) with peak 5-FU levels occurring slightly later, at 2 hours.

ADVERSE EFFECTS

The following is the list of clinically relevant adverse events seen in 5% of patients, where capecitabine was used either as monotherapy or in combination in patients with colon cancer and breast cancer.

Gastrointestinal Disorders: diarrhoea, nausea, stomatitis, vomiting, abdominal pain, constipation, upper abdominal pain, dyspepsia, gastrointestinal haemorrhage, ileus, dry mouth.

Skin and Subcutaneous Tissue Disorders: hand-and-foot syndrome, alopecia, rash, erythema, pruritus, dermatitis.

General Disorders: fatigue, pyrexia, asthenia, lethargy, oedema, chest pain, back pain, arthralgia.

Nervous System Disorders: peripheral sensory neuropathy, dizziness, headache, taste disturbance, insomnia, mood alteration, depression.

Eye Disorders: conjunctivitis

Blood and Lymphatic System Disorders: anaemia, neutropenia, decreased platelets.

Respiratory Thoracic and Mediastinal Disorders: epistaxis, dyspnoea, cough, sore throat.

Metabolism: appetite decreased, dehydration.

Eye: eye irritation, vision abnormality.

Musculoskeletal: back pain, arthralgia.

Hepatobiliary: hyperbilirubinemia.

The clinically relevant adverse events in < 5% of patients with breast and colon cancers treated with capecitabine monotherapy are shown below. In parentheses is the incidence of grade 3 or 4 occurrences of each adverse event.

Gastrointestinal: abdominal distension, dysphagia, proctalgia, ascites (0.1), gastric ulcer (0.1), ileus (0.3), toxic dilation of intestine, gastroenteritis (0.1).

Skin and Subcutaneous: nail disorder (0.1), sweating increased (0.1), photosensitivity reaction (0.1), skin ulceration, pruritus, radiation recall syndrome (0.2).

General: chest pain (0.2), influenza-like illness, hot flushes, pain (0.1), hoarseness, irritability, difficulty in walking, thirst, chest mass, collapse, fibrosis (0.1), haemorrhage, oedema, sedation.

Neurological: insomnia, ataxia (0.5), tremor, dysphasia, encephalopathy (0.1), abnormal co-ordination, dysarthria, loss of consciousness (0.2), impaired balance.

Metabolism: increased weight, cachexia (0.4), hypertriglyceridemia (0.1), hypokalemia, hypomagnesaemia.

Eye: conjunctivitis.

Respiratory: cough (0.1), epistaxis (0.1), asthma (0.2), haemoptysis, respiratory distress (0.1), dyspnoea.

Cardiac: tachycardia (0.1), bradycardia, atrial fibrillation, ventricular extrasystoles, extrasystoles, myocarditis (0.1), pericardial effusion.

Infections: laryngitis (1.0), bronchitis (0.2), pneumonia (0.2), bronchopneumonia (0.2), keratoconjunctivitis, sepsis (0.3), fungal infections (including candidiasis) (0.2).

Musculoskeletal: myalgia, bone pain (0.1), arthritis (0.1), muscle weakness.

Blood and Lymphatic: leukopenia (0.2), coagulation disorder (0.1), bone marrow depression (0.1), idiopathic thrombocytopenia purpura (1.0), pancytopenia (0.1).

Vascular: hypotension (0.2), hypertension (0.1), lymphoedema (0.1), pulmonary embolism (0.2), cerebrovascular accident (0.1).

Psychiatric: depression, confusion (0.1).

Renal: renal impairment (0.6).

Ear: vertigo.

DRUG INTERACTIONS

Drug-Food Interaction

In all clinical trials, patients were instructed to administer Capecitabine within 30 minutes after a meal. Since current safety and efficacy data are based upon administration with food, it is recommended that Capecitabine be administered with food.

Drug-Drug Interactions

Antacid

The effect of an aluminum hydroxide- and magnesium hydroxide-containing antacid was a small increase in plasma concentrations of Capecitabine and one metabolite (5'-DFCR); there was no effect on the 3 major metabolites (5'-DFUR, 5-FU and FBAL).

Anticoagulants

Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly. Altered coagulation parameters and/or bleeding have been reported in patients taking Capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred in patients with and without liver metastases. In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Phenytoin

The level of phenytoin should be carefully monitored in patients taking Capecitabine and phenytoin dose may need to be reduced. Post-marketing reports indicate that some patients receiving Capecitabine and phenytoin had toxicity associated with elevated phenytoin levels. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine and/or its metabolites.

Leucovorin

The concentration of 5-fluorouracil is increased and its toxicity may be enhanced by leucovorin. Deaths from severe enterocolitis, diarrhoea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil.

WARNINGS

Renal Insufficiency

Patients with moderate renal impairment at baseline require dose reduction. Patients with mild and moderate renal impairment at baseline should be carefully monitored for adverse events. Prompt interruption of therapy with subsequent dose adjustments is recommended if a patient develops a grade 2 to 4 adverse event.

Coagulopathy

Altered coagulation parameters and/or bleeding have been reported in patients taking Capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred in patients with and without liver metastases. In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Diarrhoea

Capecitabine can induce diarrhoea, sometimes severe. Patients with severe diarrhoea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. If grade 2, 3 or 4 diarrhoea occurs, administration of Capecitabine should be immediately interrupted until the diarrhoea resolves or decreases in intensity to grade 1. Following a re-occurrence of grade 2 diarrhoea or occurrence of any grade 3 or 4 diarrhoea, subsequent doses of Capecitabine should be decreased. Standard anti-diarrhoeal treatments are recommended. Necrotizing enterocolitis (typhlitis) has been reported.

Hand-and-Foot Syndrome

Hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema) is a cutaneous toxicity. Median time to onset was 79 days (range from 11 to 360 days) with a severity range of grades 1 to 3 for patients receiving Capecitabine monotherapy in the metastatic setting. Grade 1 is characterized by any of the following: numbness, dysesthesia/paresthesia, tingling, painless swelling or erythema of the hands and/or feet and/or discomfort which does not disrupt normal activities. 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 or 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 Capecitabine should be interrupted until the event resolves or decreases in intensity to grade 1. Following grade 3 hand-and-foot syndrome, subsequent doses of Capecitabine should be decreased.

Geriatric Patients

Patients 80 years old may experience a greater incidence of grade 3 or 4 adverse events. Among the patients 60 years of age receiving Capecitabine

in combination with docetaxel, the incidence of grade 3 or 4 treatment-related adverse events, treatment-related serious adverse events, withdrawals due to adverse events, treatment discontinuations due to adverse events and treatment discontinuations within the first two treatment cycles was higher than in the < 60 years of age patient group.

Pregnancy

Capecitabine may cause foetal harm when given to a pregnant woman. There are no adequate and well-controlled studies in pregnant women using Capecitabine. 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 foetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Capecitabine.

PRECAUTIONS

General

Patients receiving therapy with Capecitabine 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.

Cardiotoxicity

The cardiotoxicity observed with Capecitabine includes myocardial infarction/ischaemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse events may be more common in patients with a prior history of coronary artery disease.

Dihydropyrimidine Dehydrogenase Deficiency

Rarely, unexpected, severe toxicity (eg, stomatitis, diarrhoea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. A link between decreased levels of DPD and increased, potentially fatal toxic effects of 5-fluorouracil therefore cannot be excluded.

Hepatic Insufficiency

Patients with mild to moderate hepatic dysfunction due to liver metastases should be carefully monitored when Capecitabine is administered. The effect of severe hepatic dysfunction on the disposition of Capecitabine is not known.

Hyperbilirubinemia

If drug-related grade 2 to 4 elevations in bilirubin occur, administration of Capecitabine 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 to 3 x normal and grade 4 hyperbilirubinemia as > 3 x normal.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Adequate studies investigating 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 foetuses 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 spermatozoa and spermatozoa.

OVERDOSE

The manifestations of acute overdose would include nausea, vomiting, diarrhoea, 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.

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 known hypersensitivity to 5-fluorouracil. Capecitabine is contraindicated in patients with known dihydropyrimidine dehydrogenase (DPD) deficiency. Capecitabine is also contraindicated in patients with severe renal impairment (creatinine clearance below 30 mL/min).

HOW SUPPLIED

Capecitabine is supplied as film-coated tablets containing 500 mg in strip of ten.

Storage Conditions

Store in a cool, dry place. Protect from light. Excursions of storage temperature not to exceed 30 degree C.

Shelf life

18 months.



Reliance Life Sciences Pvt. Ltd.