oncogen

Pectibine Capecitabine 500mg

پیکٹیبین
(کیپسیٹابین)

WARNING: INCREASED RISK OF BLEEDING WITH CONCOMITANT USE OF VITAMIN K ANTAGONISTS
See full prescribing information for complete boxed warning.
Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with oral vitamin K antagonists. Monitor international normalized ratio (INR) more frequently and adjust the dose of the vitamin K antagonist as appropriate.

1. NAME OF THE MEDICINAL PRODUCT
Pectibine 500 mg film-coated tablets
2.QUALITATIVE AND QUANTITATIVE COMPOSITION:
Each film-coated tablet contains capecitabine 500mg.
3. PHARMACEUTICAL FORM
Film-coated tablet.
The film-coated tablets are peach tablets of biconvex, oblong shape with the marking '500' on the one side and 'C' on the other side.
4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Colorectal Cancer
Patients with stage III colon cancer as an adjuvant treatment or patients with unresectable or metastatic colorectal cancer as a single agent or as part of combination chemotherapy regimen.
In Locally advanced rectal cancer as a component of chemoradiotherapy.
Breast Cancer
Patients of advanced or metastatic breast cancer where an anthracycline or taxane-containing chemotherapy is not indicated or in combination with docetaxel after disease progression on prior anthracycline containing chemotherapy.
Gastric, Esophageal, or Gastroesophageal Junction Cancer
Adult patient of unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer or treatment of adults with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease as a component of a combination regimen.
Pancreatic Cancer
Adult patients with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen.
4.2 Posology or Method of Administration
Capecitabine should only be prescribed by a qualified physician experienced in the utilization of antineoplastic medicinal products. Careful monitoring during the first cycle of treatment is recommended for all patients.
Adjuvant Treatment of Colon Cancer
Single agent: 1,250 mg/m^2 twice daily orally for the first 14 days of each 21-day cycle for a maximum of 8 cycles. In combination with Oxaliplatin-Containing Regimens: 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle for a maximum of 8 cycles in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.Perioperative Treatment of Rectal Cancer:
(a) With Concomitant Radiation Therapy: 825 mg/m^2 orally twice daily) (b) Without Radiation Therapy: 1,250 mg/m^2 orally twice daily.
Unresectable or Metastatic Colorectal Cancer
Single agent: 1,250 mg/m^2 twice daily orally for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity. In Combination with Oxaliplatin: 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.
Advanced or Metastatic Breast Cancer
Single agent: 1,000 mg/m^2 or 1,250 mg/m^2 twice daily orally for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity. In combination with docetaxel: 1,000 mg/m^2 or 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle, until disease progression or unacceptable toxicity in combination with docetaxel at 75 mg/m^2 administered intravenously on day 1 of each cycle.
Unresectable or Metastatic Gastric, Esophageal, or Gastroesophageal Junction Cancer
625 mg/m^2 orally twice daily on days 1 to 21 of each 21-day cycle for a maximum of 8 cycles in combination with platinum-containing chemotherapy OR 850 mg/m^2 or 1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with oxaliplatin 130 mg/m^2 administered intravenously on day 1 of each cycle.
HER2-overexpressing metastatic adenocarcinoma of the gastroesophageal junction or stomach
1,000 mg/m^2 orally twice daily for the first 14 days of each 21-day cycle until disease progression or unacceptable toxicity in combination with cisplatin and trastuzumab.
Pancreatic cancer
830 mg/m^2 orally twice daily for the first 21 days of each 28-day cycle for maximum of 6 cycles in combination with gemcitabine 1,000 mg/m^2 administered intravenously on days 1, 8, and 15 of each cycle.
Capecitabine dose calculation
Table 1 Standard and reduced dose calculations according to body surface area for a starting dose of

	Does Level 1250 mg/m^2 (twice daily)				
	Full dose 1250mg/m^2	Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)		Reduced dose (75%) 950 mg/m^2	Reduced dose (50%) 625 mg/m^2
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤1.26	1500	-	3	1150	800
1.27 - 1.38	1650	1	3	1300	800
1.39 - 1.52	1800	2	3	1450	950
1.53 - 1.66	2000	-	4	1500	1000
1.67 - 1.78	2150	1	4	1650	1000
1.79 - 1.92	2300	2	4	1800	1150
1.93 - 2.06	2500	-	5	1950	1300
2.07 - 2.18	2650	1	5	2000	2000
≥2.19	2800	2	5	2150	1450

Table 2 Standard and reduced dose calculations according to body surface area for a starting dose of Capecitabine of 1000 mg/m^2

	Does Level 1250 mg/m^2 (twice daily)				
	Full dose 1000mg/m^2	Number of 150 mg tablets and/or 500 mg tablets per administration (each administration to be given morning and evening)		Reduced dose (75%) 750 mg/m^2	Reduced dose (50%) 500 mg/m^2
Body Surface Area (m^2)	Dose per administration (mg)	150 mg	500 mg	Dose per administration (mg)	Dose per administration (mg)
≤1.26	1500	1	2	800	600
1.27 - 1.38	1300	2	2	1000	600
1.39 - 1.52	1450	3	2	1100	750
1.53 - 1.66	1600	4	2	1200	800
1.67 - 1.78	1750	5	2	1300	800
1.79 - 1.92	1800	2	3	1400	900
1.93 - 2.06	2000	-	4	1500	1000
2.07 - 2.18	2150	1	4	1600	1050
≥2.19	2300	2	4	1750	1100

4.3 Dose Modifications
Monitor patients for adverse reactions and modify dosages of capecitabine as described in Table 1, 2 & 3. Do not replace missed doses instead resume capecitabine with the next planned dosage. When capecitabine is administered with docetaxel, withhold capecitabine and docetaxel until the requirements for resuming both capecitabine and docetaxel are met. Refer to the Prescribing Information for docetaxel for additional dosing information as appropriate.

Table 3 Capecitabine Dose Reduction Schedule (3-weekly Cycle or Continuous Treatment)

Toxicity grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% 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		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
• Grade 3		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
• 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%
-2nd appearance	Discontinue permanently	Not applicable

4.4 Dose Modification for Special Population
Hyperbilirubinemia: Patients with Grade 3-4 hyperbilirubinemia may resume treatment once the event is Grade 2 or less (less than three times the upper limit of normal), using the percent of current dose as shown in column 3 of Table 1.
Renal Impairment: Reduce the dose of Capecitabine by 25% for patients with creatinine clearance (CLcr) of 30 to 50 mL/min as determined by Cockcroft-Gault equation. A dosage has not been established in patients with severe renal impairment (CLcr <30 mL/min).
4.5 Administration
Swallow Capecitabine tablets whole with water within 30 minutes after a meal. Do not chew, cut, or crush capecitabine tablets.Take capecitabine at the same time each day approximately 12 hours apart. Do not take an additional dose after vomiting and continue with the next scheduled dose. Do not take a missed dose and continue with the next scheduled dose. Capecitabine is a hazardous drug. Follow applicable special handling and disposal procedures.
4.6 Contraindications
It is contraindicated in patients with history of severe hypersensitivity reaction to fluorouracil or capecitabine. (see adverse drug reactions)
4.7 Warning and Precautions
Increased Risk of Bleeding with Concomitant Use of Vitamin K Antagonists
Studies have shown clinically significant increases in PT and INR in patients who were on stable doses of oral vitamin K antagonists at the time capecitabine was introduced. These events occurred within several days and up to several months after initiating capecitabine and, in a few cases, within 1 month after stopping capecitabine. These events occurred in patients with and without liver metastases.

Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency
Capecitabine is not recommended for use in patients known to have certain homozygous or compound heterozygous DPYD variants that result in complete DPD deficiency. Withhold or permanently discontinue capecitabine based on clinical assessment of the onset, duration, and severity of the observed adverse reactions in patients with evidence of acute early onset or unusually severe reactions, which may indicate complete DPD deficiency. There are insufficient data to recommend a specific dose in patients with partial DPD deficiency.
Cardiotoxicity
Myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy have been reported with capecitabine. These adverse reactions may be more common in patients with a prior history of coronary artery disease. Withhold capecitabine for cardiotoxicity as appropriate. The safety of resumption of capecitabine in patients with cardiotoxicity that has resolved have not been established.
Diarrhea
In a study with 875 patients with metastatic breast or colorectal cancer who received capecitabine as a single agent, the median time to first occurrence of grade 2 to 4 diarrhea was 34 days (range: 1 day to 1 year). The median duration of grade 3 to 4 diarrhea was 5 days. Withhold capecitabine and resume at same or reduced dose or permanently discontinue based on severity and occurrence.
Dehydration
Dehydration can occur with capecitabine. Optimize hydration before starting capecitabine. Monitor hydration status and kidney function at baseline and as clinically indicated.
Renal Toxicity
Renal impairment or coadministration of capecitabine with other products known to cause renal toxicity may increase the risk of renal toxicity. Monitor renal function at baseline and as clinically indicated. Optimize hydration before starting capecitabine
Serious Skin Toxicities
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome and toxic epidermal necrolysis (TEN), which can be fatal, can occur with capecitabine. Monitor for new or worsening serious skin reactions. In case of severe cutaneous adverse reactions permanently discontinue capecitabine.
Palmar-Plantar Erythrodysesthesia Syndrome (PPES)
In a study of patients with metastatic breast or colorectal cancer who received capecitabine as a single agent, the median time to onset of grades 1 to 3 PPES was 2.6 months (range: 11 days to 1 year). Withhold capecitabine and resume at same or reduced dose or permanently discontinue based on severity and occurrence.
Myelosuppression
Myelosuppression can occur with capecitabine. Monitor complete blood count at baseline and before each cycle. Capecitabine is not recommended if baseline neutrophil count <1.5 x 10^9/L or platelet count <100 x 10^9/L. For grade 3 to 4 myelosuppression, withhold capecitabine and then resume at same or reduced dose, or permanently discontinue, based on occurrence.
Hyperbilirubinemia
Hyperbilirubinemia can occur with capecitabine. Patients with Grade 3-4 hyperbilirubinemia may resume treatment once the event is Grade 2 or less than three times the upper limit of normal, using the percent of current dose as shown in Table 1, 2 & 3 (see 4.3 : Dose modification)
Embryo-Fetal Toxicity
Insufficient data is available on capecitabine use in pregnant women to evaluate a drug-associated risk. Advise pregnant women of the potential risk to a fetus.
Other Adverse Reactions from Exposure to Crushed Tablets
The safety and effectiveness have not been established for the administration of crushed capecitabine tablets. If capecitabine tablets must be cut or crushed, this should be done by a professional trained in safe handling of cytotoxic.
4.8 Effects on ability to drive and use machines
Capecitabine has minor or moderate influence on the ability to drive and use machines. Capecitabine may cause dizziness, fatigue and nausea
4.9 Interactions with other medicinal products
Effect of Other Drugs on Capecitabine
Allopurinol: Avoid Concomitant use with allopurinol as it may decrease concentration of capecitabine's active metabolites which may decrease efficacy.
Leucovorin: The concentration of fluorouracil is increased and its toxicity may be enhanced by leucovorin, folic acid, or folate analog products. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil. Instruct patients not to take products containing folic acid or folate analog products unless directed to do so by their healthcare provider.
Effect of Capecitabine on Other Drugs
CYP2C9 Substrates: Capecitabine increased exposure of CYP2C9 substrates may increase the risk of adverse reactions related to these substrates. Closely monitor for adverse reactions in patient with who are concomitantly using drugs like anti coagulants, antidiabetics with capecitabine.
Vitamin K Antagonists: Capecitabine increases exposure of vitamin K antagonist. Monitor INR more frequently and refer to the prescribing information of oral vitamin K antagonist for dosage adjustment, as appropriate, when capecitabine is used concomitantly with vitamin K antagonist (See 6.1).
Phenytoin: Capecitabine may increase exposure of phenytoin, which may increase the risk of adverse reactions related to phenytoin. Closely monitor phenytoin levels and refer to the prescribing information of phenytoin for dose adjustment, as appropriate when capecitabine is used concomitantly with phenytoin.
Nephrotoxic Drugs: Concomitant use of capecitabine with other drugs known to cause renal toxicity may increase the risk of renal toxicity. Closely monitor for signs of renal toxicity when capecitabine is used concomitantly with nephrotoxic drugs e.g., platinum salts, irinotecan, methotrexate, intravenous bisphosphonates. (See 4.4)
4.10 Fertility, pregnancy and lactation
Fertility
Advise females of reproductive potential to use effective contraception during treatment with capecitabine and for 6 months after the last dose.
Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with capecitabine and for 3 months after the last dose.
Infertility
Based on animal studies, capecitabine may impair fertility in females and males of reproductive potential
Pregnancy
Based on findings in animal reproduction studies and its mechanism of action, capecitabine can cause fetal harm when administered to a pregnant woman. Available human data with capecitabine use in pregnant women is not sufficient to inform the drug-associated risk. Verify pregnancy status in females of reproductive potential prior to initiating capecitabine as it can cause fetal harm when administered to a pregnant woman.
Lactation
There is no information regarding the presence of capecitabine or its metabolites in human milk, or on its effects on milk production or the breastfed child. In animal studies, Capecitabine metabolites were present in the milk of lactating mice. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with capecitabine and for 1 week after the last dose.
4.11 Pediatric Use
The safety and effectiveness of capecitabine in pediatric patients have not been established.
Geriatric Use
No overall differences in efficacy were observed comparing older versus younger patients with colorectal cancer, gastric, esophageal or gastrointestinal junction cancer, or pancreatic cancer using the approved recommended dosages and treatment regimens. Older patients experience increased gastrointestinal toxicity due to Capectiabine compared to younger patients. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil.
4.12 Undesirable effects
Summary of the safety profile
The overall safety profile of capecitabine is based on data from over 3000 patients treated with capecitabine as monotherapy or capecitabine in combination with different chemotherapy regimens in multiple indications.

The safety profiles of capecitabine monotherapy for the metastatic breast cancer, metastatic colorectal cancer and adjuvant colon cancer populations are comparable. The most commonly reported and/or clinically relevant treatment-related adverse drug reactions (ADRs) were gastrointestinal disorders (especially diarrhoea, nausea, vomiting, abdominal pain, stomatitis), hand-foot syndrome (palmar-plantar erythrodysesthesia), fatigue, asthenia, anorexia, cardiotoxicity, increased renal dysfunction on those with preexisting compromised renal function, and thrombosis/embolism.

Tabulated list of adverse reactions

ADRs considered by the investigator to be possibly, probably, or remotely related to the administration of capecitabine are listed in table 4 for capecitabine given as monotherapy and in table 5 for capecitabine given in combination with different chemotherapy regimens in multiple indications.

The following headings are used to rank the ADRs by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Capecitabine Monotherapy: Table 4 lists ADRs associated with the use of capecitabine monotherapy based on a pooled analysis of safety data from three major studies including over 1900 patients.

Body System	Very Common All grades	Common All grades	Uncommon Severe and/or Life-threatening (grade 3-4) or considered medically relevant	Rare/Very Rare (Post-Marketing Experience)
Infections and infestations	-	Herpes viral infection, Nasopharyngitis, Lower respiratory tract infection	Sepsis, Urinary tract infection, Cellulitis, Tonsillitis, Pharyngitis, Oral candidiasis, Influenza,Gastroenteritis, Fungal infection, Infection, Tooth abscess	-
Neoplasm benign, malignant and unspecified	-	-	Lipoma	-
Blood and lymphatic system disorders	-	Neutropenia, Anaemia	Febrile neutropenia, Pancytopenia, Granulocytopenia, Thrombocytopenia, Leukopenia, Haemolytic anaemia, International Normalised Ratio (INR) increased/Prothrombin time prolonged	-
Immune system disorders	-	-	Hypersensitivity	Angioedema (rare)
Metabolism and nutrition disorders	Anorexia	Dehydration, Weight decreased	Diabetes, Hypokalaemia, Appetite disorder, Malnutrition, Hypertriglyceridaemia	-
Psychiatric disorders	-	Insomnia, Depression	Confusional state, Panic attack, Depressed mood, Libido decreased	-
Nervous system disorders	-	Headache, Lethargy Dizziness, Parasthesia Dysgeusia	Aphasia, Memory impairment, Ataxia, Syncope, Balance disorder, Sensory disorder, Neuropathy peripheral	Toxic leukoencephalopathy (very rare)
Eye disorders	-	Lacrimation increased, Conjunctivitis, Eye irritation	Visual acuity reduced, Diplopia	Lacrimal duct stenosis (rare), Corneal disorders(rare),
Ear and labyrinth disorders	-	-	Vertigo, Ear pain	-
Cardiac disorders	-	-	Angina unstable, Angina pectoris, Myocardial ischaemia/infarction, Atrial fibrillation, Arrhythmia, Tachycardia, Sinus tachycardia, Palpitations	(rare), Torsade de pointes (rare), Bradycardia (rare), Vasospasm (rare)
Vascular disorders	-	Thrombophlebitis	Deep vein thrombosis, Hypertension, Petechiae, Hypotension, Hot flush, Peripheral coldness	-
Respiratory, thoracic and mediastinal disorders	-	Dyspnoea, Epistaxis, Cough, Rhinorrhoea	Pulmonary embolism, Pneumothorax, Haemoptysis, Asthma, Dyspnoea exertional	-
Gastrointestinal disorders	Diarrhoea, Vomiting, Nausea,	Gastrointestinal haemorrhage, Constipation, Upper abdominal pain, Dyspepsia, Flatulence, Dry mouth	Intestinal obstruction, Ascites, Enteritis, Gastritis, Dysphagia, Abdominal pain lower, Oesophagitis, Abdominal discomfort, Gastrooesophageal reflux disease, Colitis, Blood in stool	-
Hepatobiliary disorders	-	Hyperbilirubinaemia, Liver function test abnormalities	Jaundice	Hepatic failure (rare), Cholestatic hepatitis (rare)
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysaesthesia syndrome**	Rash, Alopecia, Erythema, Dry skin, Pruritus, Skin hyper-pigmentation, Rash macular, Skin desquamation, Dermatitis, Pigmentation disorder, Nail disorder	Blister, Skin ulcer, Rash, Urticaria, Photosensitivity reaction, Palmar erythema, Swelling face, Purpura, Radiation recall syndrome	Cutaneous lupus erythematosus (rare), Severe skin reactions such as Stevens-Johnson Syndrome and toxic Epidermal Necrolysis (very rare) (see section 4.4.)
Musculoskeletal and connective tissue disorders	-	Pain in extremity, Back pain, Arthralgia	Joint swelling, Bone pain, Facial pain, Musculoskeletal stiffness, Muscular weakness	-
Renal and urinary disorders	-	-	Hydronephrosis, Urinary incontinence, Haematuria, Nocturia, Blood creatinine increased	-
Reproductive system and breast disorders	-	-	Vaginal haemorrhage	-
General disorders and administration site conditions	Fatigue, Asthenia	Pyrexia, Oedema peripheral, Malaise, Chest pain	Oedema, Chills, Influenza like illness, Rigors, Body temperature increased	-

Based on the post-marketing experience, persistent or severe palmar-plantar erythrodysaesthesia syndrome can eventually lead to loss of fingerprints

Capecitabine in combination therapy:

Table 5 lists ADRs associated with the use of capecitabine in combination with different chemotherapy regimens in multiple indications based on safety data from over 3000 patients. ADRs are added to the appropriate frequency grouping (Very common or Common) according to the highest incidence seen in any of the major clinical trials and are only added when they were seen in addition to those seen with capecitabine monotherapy or seen at a higher frequency grouping compared to capecitabine monotherapy (see table 4).

Some of the ADRs are reactions commonly seen with the combination medicinal product (e.g. peripheral sensory neuropathy with docetaxel or oxaliplatin, hypertension seen with bevacizumab); however an exacerbation by capecitabine therapy cannot be excluded.

Body System	Very Common All grades	Common All grades	Rare/Very Rare (Post-Marketing Experience)
Infections and infestations	-	Herpes zoster, Urinary tract infection, Oral candidiasis, Upper respiratory tract infection, Rhinitis, Influenza, +Infection, Oral herpes	-
Blood and lymphatic system disorders	+Neutropenia, +Leucopenia, +Anaemia, +Neutropenic fever, Thrombocytopenia	Bone marrow depression, +Febrile Neutropenia	-
Immune system disorders	Appetite decreased	Hypersensitivity	
Metabolism and nutrition disorders	Appetite decreased	Hypokalaemia,Hyponatraemia, Hypomagnesaemia, Hypocalcaemia, Hyperglycaemia	-
Psychiatric disorders	Psychiatric disorders	Sleep disorder, Anxiety	-
Nervous system disorders	Paraesthesia, Dysaesthesia, Peripheral neuropathy, Peripheral sensory neuropathy, Dysgeusia, Headache	Neurotoxicity, Tremor, Neuralgia, Hypersensitivity reaction, Hypoaesthesia	-
Eye disorders	Eye disorders	Visual disorders, Dry eye, Eye pain, Visual impairment, Vision blurred	-
Ear and labyrinth disorders	-	Tinnitus, Hypoacusis	-
Cardiac disorders	-	Atrial fibrillation, Cardiac ischaemia/infarction	-
Vascular disorders	Lower limb oedema, Hypertension, +Embolism and thrombosis	Flushing, Hypotension, Hypertensive crisis, Hot flush, Phlebitis	-
Respiratory, thoracic and mediastinal system disorders	Sore throat, Dysaesthesia pharynx	Hiccups, Pharyngolaryngeal pain, Dysphonia	-
Gastrointestinal disorders	Constipation, Dyspepsia	Upper gastrointestinal haemorrhage, Mouth ulceration, Gastritis, Abdominal distension, Gastroesophageal reflux disease, Oral pain, Dysphagia, Rectal haemorrhage, Abdominal pain lower, Oral dysaesthesia, Paraesthesia oral, Hypoaesthesia oral, Abdominal discomfort	-
Hepatobiliary disorders	-	Hepatic function abnormal	-
Skin and subcutaneous tissue disorders	Alopecia, Nail disorder	Hyperhidrosis, Rash erythematous, Urticaria, Night sweats	-
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity	Pain in jaw , Muscle spasms, Trismus, Muscular weakness	-
Renal and urinary disorder	-	Haematuria, Proteinuria, Creatinine renal clearance decreased, Dysuria	Acute renal failure secondary to dehydration (rare)
General disorders and administration	Pyrexia, Weakness, +Lethargy, Temperature intolerance	Mucosal inflammation, Pain in limb, Pain, Chills, Chest pain, Influenza-like illness, +Fever, Infusion related reaction, Injection site reaction, Infusion site pain, Injection site pain	-
Injury, poisoning and procedural complications	-	Contusion	-

+ For each term, the frequency count was based on ADRs of all grades. For terms marked with a "+", the frequency count was based on grade 3-4 ADRs. ADRs are added according to the highest incidence seen in any of the major combination trials.

Overdosage

Administer uridine triacetate within 96 hours for management of capecitabine overdose. 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: cytostatic (antimetabolite), ATC code: L01BC06.

5.1 Mechanism of Action

Capecitabine is metabolized to fluorouracil in vivo. Both normal and tumor cells metabolize fluorouracil 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, N5-10-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.

5.2 Pharmacodynamics

Population-based exposure-effect analyses demonstrated a positive association between AUC of fluorouracil and grade 3-4 hyperbilirubinemia.

5.3 Pharmacokinetics

The AUC of capecitabine and its metabolite 5'-DFCR increases proportionally over a dosage range of 500mg/m^2/day to 3,500 mg/m^2/day (0.2 to 1.4 times the approved recommended dosage). The AUC of capecitabine's metabolites 5'-DFUR and fluorouracil increased greater than proportional to the dose. The interpatient variability in the C_{max} and AUC of fluorouracil was greater than 85%.

Absorption

Following oral administration of capecitabine 1,255 mg/m^2 orally twice daily (the recommended dosage when used as single agent), the median Tmax of capecitabine and its metabolite fluorouracil was approximately 1.5 hours and 2 hours, respectively.

Effect of Food

Following administration of a meal (breakfast medium-rich in fat and carbohydrates), the mean Cmax and $AUC^{0\text{-}INF}$ of capecitabine was decreased by 60% and 34%, respectively. The mean Cmax and $AUC^{0\text{-}INF}$ of fluorouracil were also decreased by 37 % and 12%, respectively. The Tmax of both capecitabine and fluorouracil was delayed 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%).Following oral administration of capecitabine 7 days before surgery in patients with colorectal cancer, the median ratio of concentration for the active metabolite fluorouracil in colorectal tumors to adjacent tissues was 2.9 (range: 0.9 to 8.0).

Elimination

The elimination half-lives of capecitabine and fluorouracil were approximately 0.75 hour.

Metabolism Capecitabine undergoes metabolism by carboxylesterase and is hydrolyzed to 5'-DFCR. 5' DFCR is subsequently converted to 5'-DFUR by cytidine deaminase. 5'-DFUR is then hydrolized by thymidine phosphorylase (dThdPase) enzymes to the active metabolite fluorouracil. Fluorouracil is subsequently metabolized by dihydropyrimidine dehydrogenase to 5-fluoro-5, 6 dihydro-fluorouracil (FUH2). The pyrimidine ring of FUH2 is cleaved by dihydropyrimidinase to yield 5-fluoro-ureido-propionic acid (FUPA). Finally, FUPA is cleaved by β-ureido-propionase to α-fluoro-β-alanine (FBAL).

Excretion Following administration of radiolabeled capecitabine, 96% of the administered capecitabine dose was recovered in urine (3% unchanged and 57% as metabolite FBAL) and 2.6% in feces

5.4 Specific Populations

Patients with Renal Impairment

Table 6 Effect of Renal Impairment on the Pharmacokinetics of Capecitabine, 5'-DFUR, and FBAL

Table 6 Effect of Renal Impairment on the Pharmacokinetics of Capecitabine, 5'-DFUR, and FBAL Renal Impairment	Changes in AUC			
	Capecitabine	5'-DFURc	FBALc	5-FU
CLcr 30 to 50 mL/min	Increased by 25%	Increased by 42%	Increased by 85%	No relevant change
CLcr <30 mL/min	Increased by 25%	Increased by 71%	Increased by 258%	Increased by 24%

Compared to patients with CLcr >80 mL/min Following administration of capecitabine 1,250 mg/m^2 orally twice daily; day 1 observations Capecitabine metabolite CLcr= Creatine Clearance, AUC= Area under the plasma concentration-time curve

Patients with Hepatic Impairment

$AUC^{0\text{-}INF}$ and C_{max} of capecitabine's active principle, fluorouracil, were not affected in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. The $AUC^{0\text{-}INF}$ and of capecitabine increased by 60%. The effect of severe hepatic impairment on the pharmacokinetics of capecitabine and its metabolites are unknown.

Pharmacogenomics

The DPYD gene encodes the enzyme DPD, which is responsible for the catabolism of >80% of fluorouracil. Patients who are homozygous or compound heterozygous for no function DPYD variants (i.e., carry two no function DPYD variants) or are compound heterozygous for a no function DPYD variant plus a decreased function DPYD variant have complete DPD deficiency and are at increased risk for acute early-onset of toxicity and serious life-threatening, or fatal adverse reactions due to increased systemic exposure to capecitabine. Patients with partial DPD deficiency may also be at an increased risk for toxicity from capecitabine.

6. PHARMACEUTICAL PARTICULARS

6.1 Pack Size

12x 10's (120) tablets.

Alu/Alu blisters having 10 tablets in each blister and packed in unit carton with leaflet

6.2 Storage Conditions

Store below 30°C, Protect from sunlight and moisture.

6.3 Dosage and Instructions

As directed by physician.

Keep out of reach of children.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

For adverse event reporting, kindly email us at
pharmacovigilance@oncogenpharma.com.pk

7. MANUFACTURER

Manufactured by:

oncogen

Oncogen Pharma (Pvt.) Limited.
Plot No: WH-26 & 27-A3, Korangi Creek
Industrial Park (KCIP), Karachi 75190, Pakistan.
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