Prescribing information:
Xelodace DT (Capecitabine dispersible tablets)
1. Generic name:
Capecitabine Dispersible tablets 1000 mg
Capecitabine Dispersible tablets 500 mg

2. Qualitative and quantitative composition:
Capecitabine Dispersible tablets 1000 mg:
Each uncoated dispersible tablet contains 1000 mg capecitabine.
Capecitabine Dispersible tablets 500 mg:
Each uncoated dispersible tablet contains 500 mg capecitabine.

3. Dosage form and strength:
Dosage form: Uncoated Dispersible tablets
Strength: 1000 mg & 500 mg

4. INDICATIONS AND USAGE:
XELODACE DT (capecitabine Dispersible tablet) is a nucleoside metabolic inhibitor indicated for:
4.1 Colorectal Cancer
• Adjuvant treatment of patients with Stage III colon cancer as a single agent or as a component of a combination chemotherapy regimen.
• Perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy.
• Treatment of patients with unresectable or metastatic colorectal cancer as a single agent or as a component of a combination chemotherapy regimen.
4.2 Breast Cancer
• treatment of patients with advanced or metastatic breast cancer as a single agent if an anthracycline- or taxane-containing chemotherapy is not indicated.
• treatment of patients with advanced or metastatic breast cancer in combination with docetaxel after disease progression on prior anthracycline-containing chemotherapy.
4.3 Gastric, Esophageal, or Gastroesophageal Junction Cancer
• treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen.
• 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.
4.4 Pancreatic Cancer
•adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen.

5. DOSAGE AND ADMINISTRATION:
5.1 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 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.
5.2 Perioperative Treatment of Rectal Cancer
• With Concomitant Radiation Therapy: 825 mg/m^2 orally twice daily.
• Without Radiation Therapy: 1,250 mg/m^2 orally twice daily.
5.3 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.
5.4 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 1days 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.
5.5 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.
5.6 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.
5.7 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.

5.8 ADMINISTRATION: XELODACE DT is taken orally by dissolving the tablet in 100 ml of Normal water at room temperature. The complete dissolved solution to be consumed within 30 minutes.

***6.* Dose Management Guidelines**
6.1 General: Capecitabine tablets dosage may need to be individualized to optimize patient management. Patients should be carefully monitored for toxicity and doses of capecitabine tablets should be modified as necessary to accommodate individual patient tolerance to treatment. Toxicity due to capecitabine tablets administration may be managed by symptomatic treatment, dose interruptions and adjustment of capecitabine tablets dose. Once the dose has been reduced, it should not be increased later. Doses of capecitabine tablets omitted for toxicity are not replaced or restored; instead, the patient should resume the planned treatment cycles.

The dose of phenytoin and the dose of coumarin-derivative anticoagulants may need to be reduced when either drug is administered concomitantly with capecitabine tablets.

Monotherapy (Metastatic Colorectal Cancer, Adjuvant Colorectal Cancer, Metastatic Breast Cancer)
Capecitabine tablets dose modification scheme as described below (see Table 1) is recommended for the management of adverse reactions.

Table 1: Recommended Dose Modifications of Capecitabine Tablets

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 to 1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	-
Grade 3		
-1st appearance	Interrupt until resolved to grade 0 to 1	100%
-2nd appearance		75%
-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 to 1	50%

*National Cancer Institute of Canada Common Toxicity Criteria were used except for the hand-and-foot syndrome.

7. OVERDOSE & CONTRAINDICATIONS:

7.1 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/m² basis).
7.2 Contraindications:
• History of severe hypersensitivity reactions to fluorouracil or capecitabine.
• Known complete dihydropyrimidine dehydrogenase (DPD) deficiency.
• During pregnancy and lactation.
• In patients with severe leukopenia, neutropenia, or thrombocytopenia
• In patients with severe hepatic impairment.
• In patients with severe renal impairment (creatinine clearance below 30 ml/min)
• Recent or concomitant treatment with brivudine.
• If contraindications exist to any of the medicinal products in the combination regimen, that medicinal product should not be used.

8. WARNINGS AND PRECAUTIONS:
• Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency:
Patients with certain homozygous or compound heterozygous variants in the *DPYD* gene are at increased risk for acute early-onset toxicity and serious, including fatal, adverse reactions due to Capecitabine (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Capecitabine is not recommended for use in patients known to have certain homozygous or compound heterozygous *DPYD* variants that result in complete absence of DPD activity. Withhold or permanently discontinue based on clinical assessment. No capecitabine dose has been proven safe in patients

with complete absence of DPD activity.

• Cardiotoxicity: 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 has not been established.

• Diarrhea: Withhold Capecitabine and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence.

• Dehydration: Optimize hydration before starting Capecitabine. Monitor hydration status and kidney function at baseline and as clinically indicated. Withhold capecitabine and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence.

• Renal Toxicity: Monitor renal function at baseline and as clinically indicated. Optimize hydration before starting Capecitabine. Withhold capecitabine and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence.

• Serious Skin Toxicities: Monitor for new or worsening serious skin reactions. Permanently discontinue capecitabine in patients who experience a severe cutaneous adverse reaction.

• Palmar-Plantar Erythrodysesthesia Syndrome: Withhold capecitabine then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence.

• Myelosuppression: Monitor

• complete blood count at baseline and before each cycle. capecitabine is not recommended in patients with baseline neutrophil counts <1.5 x 10^9/L or platelet counts <100 x 10^9/L. For grade 3 or 4 myelosuppression, withhold capecitabine and then resume at same or reduced dose, or permanently discontinue, based on occurrence.

• Hyperbilirubinemia: Patients with Grade 3-4 hyperbilirubinemia may resume treatment once the event is Grade 2 or less (≤3 x ULN), using the percent of current dose as shown in column 3 of Table 1.

• Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.

9. ADVERSE REACTIONS:

Most common adverse reactions (≥30%) in patients with

• who received Capecitabine as a single agent for the adjuvant treatment for colon cancer were palmar-plantar erythrodysesthesia syndrome, diarrhea, and nausea.

• metastatic colorectal cancer who received capecitabine as a single agent were anemia, diarrhea, palmar-plantar erythrodysesthesia syndrome, hyperbilirubinemia, nausea, fatigue, and abdominal pain.

• metastatic breast cancer who received capecitabine with docetaxel were diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, nausea, alopecia, vomiting, edema, and abdominal pain.

• metastatic breast cancer who received Capecitabine as a single agent were lymphopenia, anemia, diarrhea, hand-and-foot syndrome, nausea, fatigue, vomiting, and dermatitis.

10. DRUG INTERACTIONS:

Allopurinol: Avoid concomitant use of allopurinol with Capecitabine.

Leucovorin: Closely monitor for toxicities when Capecitabine is coadministered with leucovorin.

CYP2C9 substrates: Closely monitor for adverse reactions when CYP2C9 substrates are coadministered with capecitabine.

Vitamin K antagonists: Monitor INR more frequently and dose adjust oral vitamin K antagonist as appropriate.

Phenytoin: Closely monitor phenytoin levels in patients taking capecitabine concomitantly with phenytoin and adjust the phenytoin dose as appropriate.

Nephrotoxic drugs: Closely monitor for signs of renal toxicity when capecitabine is used concomitantly with nephrotoxic drugs.

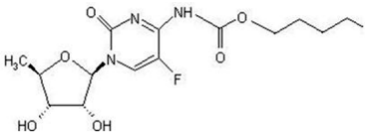
11. USE IN SPECIFIC POPULATIONS:

Lactation: Advise not to breastfeed.

Hepatic Impairment: Monitor patients with hepatic impairment more frequently for adverse reactions.

12. 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 has the following structural formula:



Capecitabine is a white to off-white crystalline powder with an aqueous solubility of 26 mg/mL at 20°C.

13. CLINICAL PHARMACOLOGY

13.1 **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.

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

13.3 **Pharmacokinetics:** The AUC of capecitabine and its metabolite 5'-DFCR increases proportionally over a dosage range of 500 mg/m^2 /day to 3,500 mg/m2 /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 Cmax and AUC of fluorouracil was greater than 85%.

13.4 **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 AUC0-INF of capecitabine was decreased by 60% and 34%, respectively. The mean Cmax and AUC0-INF of fluorouracil also decreased by 37 % and 12%, respectively. The Tmax of both capecitabine and fluorouracil was delayed by 1.5 hours.

13.5 **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).

13.6 **Elimination:** The elimination half-lives of capecitabine and fluorouracil were approximately 0.75 hour.

13.7 **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).
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.

13.8 **Specific Populations**: Following therapeutic doses of capecitabine, no clinically meaningful difference in the pharmacokinetics of 5'-DFUR, fluorouracil or FBAL were observed based on sex, age and race. No clinically ignificant differences in the pharmacokinetics of 5' DFCR, 5'-DFUR or fluorouracil were observed.

13.9 **Patients with Renal Impairment:** Effect of Renal Impairment on the Pharmacokinetics of Capecitabine, 5' DFUR, and FBAL Renal Impairment a Changes in AUC b 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 80 mL/min b Following administration of Capecitabine 1,250 mg/m2 orally twice daily; day 1 observations c Capecitabine metabolite CLcr= Creatine Clearance, AUC= Area under the plasma concentration-time curve

13.10 **Patients with Hepatic Impairment** AUC0-INF and Cmax 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 AUC0-INF and Cmax of capecitabine increased by 60%. The effect of severe hepatic impairment on the pharmacokinetics of capecitabine and its metabolites are unknown.

14 Pharmaceutical particulars

14.1 Incompatibilities

Not applicable

14.2 Packaging information

XELODACE DT is available in a strip of 10 tablets in Alu-Alu pack in a single monocarton.

14.3 STORAGE:

Store protected from light at a temperature not exceeding 30°C.

14.4 Manufactured by:

Albino Lifesciences Pvt. Ltd.
(GMP & WHO Certified company)
480/211, Harraipur, PO Gurumajra, the, Baddi. Distt- Solan (H.P) 173205.

14.5 Marketed by:

Wembrace Biopharma Pvt. Ltd.
B-6/9, Comercial complex, Safdarjung enclave,
New Delhi – 110029.
TM- Trademark applied for
R: Registered trademark
Good to Talk
Wembrace consumer care
Email: wecare@wembrace.in
Toll Free customer care: 18002029010.