CAPECITABINE - capecitabine tablet, film coated
Ascend Laboratories, LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CAPECITABINE TABLETS safely and effectively. See full prescribing information for CAPECITABINE TABLETS.
CAPECITABINE tablets, for oral use
Initial U.S. Approval: 1998

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 tablets concomitantly with oral vitamin K antagonists. (5.1, 7.2)
Monitor international normalized ratio (INR) more frequently and adjust the dose of the vitamin K antagonist as appropriate. (7.2)

RECENT MAJOR CHANGES

Boxed Warning	(12/2022)
Indications and Usage, Colorectal Cancer (1.1)	(12/2022)
Indications and Usage, Breast Cancer (1.2)	(12/2022)
Indications and Usage, Gastric, Esophageal, or Gastroesophageal Junction Cancer (1.3)	(12/2022)
Indications and Usage, Pancreatic Cancer (1.4)	(12/2022)
Dosage and Administration (2.1 to 2.7)	(12/2022)
Contraindications (4)	(12/2022)
Warnings and Precautions (5.1 to 5.12)	(12/2022)

INDICATIONS AND USAGE

Capecitabine tablets are a nucleoside metabolic inhibitor indicated for:

Colorectal Cancer

- adjuvant treatment of patients with Stage III colon cancer as a single agent or as a component of a combination chemotherapy regimen. (1.1)
- perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy. (1.1)
- treatment of patients with unresectable or metastatic colorectal cancer as a single agent or as a component of a combination chemotherapy regimen. (1.1)

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. (1.2)
- treatment of patients with advanced or metastatic breast cancer in combination with docetaxel after disease progression on prior anthracycline-containing chemotherapy. (1.2)

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. (1.3)
- 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. (1.3)

Pancreatic Cancer

- adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen. (1.4)

DOSAGE AND ADMINISTRATION

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. (2.1) 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. (2.1)

Perioperative Treatment of Rectal Cancer

- WithConcomitantRadiationTherapy:825mg/m^2 orally twice daily (2.1)
- WithoutRadiationTherapy:1,250mg/m^2 orally twice daily(2.1)

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. (2.1)
- 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. (2.1)

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. (2.2)
- 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 (2.2)

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. (2.3)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. (2.3)

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. (2.3)

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. (2.4)

Refer to Sections 2.5 and 2.6 for information related to dosage modifications for adverse reactions and renal impairment (2.5 and 2.6).

DOSAGE FORMS AND STRENGTHS

Tablets: 150 mg and 500 mg (3)

CONTRAINDICATIONS

History of severe hypersensitivity reactions to fluorouracil or capecitabine (4)

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 tablets (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Capecitabine tablets are 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 tablets dose has been proven safe in patients with complete absence of DPD activity. (5.2)
- Cardiotoxicity: May be more common in patients with a prior history of coronary artery disease. Withhold capecitabine tablets for cardiotoxicity as appropriate. The safety of resumption of capecitabine tablets in patients with cardiotoxicity that has resolved has not been established. (2.5,5.3)
- Diarrhea: Withhold capecitabine tablets and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence. (2.5, 5.4)
- Dehydration: Optimize hydration before starting capecitabine tablets. Monitor hydration status and kidney function at baseline and as clinically indicated. Withhold capecitabine tablets and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence. (2.5, 5.5)
- Renal Toxicity: Monitor renal function at baseline and as clinically indicated. Optimize hydration before starting capecitabine tablets. Withhold capecitabine tablets and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence. (2.5, 5.6)
- SeriousSkinToxicities:Monitor for new or worsening serious skin reactions. Permanently discontinue capecitabine tablets in patients who experience a severe cutaneous adverse reaction. (5.7)
- Palmar-PlantarErythrodysesthesiaSyndrome: Withhold capecitabine tablets then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence. (2.5, 5.8)
- Myelosuppression: Monitor complete blood count at baseline and before each cycle. Capecitabine tablets are 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 tablets and then resume at same or reduced dose, or permanently discontinue, based on occurrence. (2.5,5.9)
- Hyperbilirubinemia: Patients with Grade 3 to 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 (2.5,5.10)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.11,8.1,8.3)

ADVERSE REACTIONS

- Most common adverse reactions in patients who received capecitabine tablets as a single agent for the adjuvant treatment for colon cancer (≥30%) were palmar-plantar erythrodysesthesia syndrome, diarrhea, and nausea. (6.1)
- Most common adverse reactions (≥30%) in patients with metastatic colorectal cancer who received capecitabine tablets as a single agent were anemia, diarrhea, palmar-plantar erythrodysesthesia syndrome, hyperbilirubinemia, nausea, fatigue, and abdominal pain. (6.1)
- Most common adverse reactions (≥30%) in patients with metastatic breast cancer who received capecitabine tablets with docetaxel were diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, nausea, alopecia, vomiting, edema, and abdominal pain. (6.1)
- Most common adverse reactions (≥30%) in patients with metastatic breast cancer who received capecitabine tablets as a single agent were lymphopenia, anemia, diarrhea, hand-and-foot syndrome, nausea, fatigue, vomiting, and dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Ascend Laboratories, LLC at 1-877-272-7901 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Allopurinol: Avoid concomitant use of allopurinol with capecitabine tablets. (7.1)
- Leucovorin: Closely monitor for toxicities when capecitabine tablets are coadministered with leucovorin. (7.1)
- CYP2C9substrates:Closely monitor for adverse reactions when CYP2C9 substrates are coadministered with capecitabine tablets. (7.2)
- 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 tablets concomitantly with phenytoin and adjust the phenytoin dose as appropriate. (7.2)
- Nephrotoxic drugs: Closely monitor for signs of renal toxicity when capecitabine tablets are used concomitantly with nephrotoxic drugs. (7.3)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed. (8.2)
- Hepatic Impairment:Monitor patients with hepatic impairment more frequently for adverse reactions. (8.7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED RISK OF BLEEDING WITH CONCOMITANT USE OF VITAMIN K ANTAGONISTS

Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine tablets concomitantly with oral vitamin K antagonists, such as warfarin *[see Warnings and Precautions (5.1), Drug Interactions (7.2)]*.

Clinically significant increases in prothrombin time (PT) and international normalized ratio (INR) have been reported in patients who were on stable doses of a vitamin K antagonist at the time capecitabine tablets was introduced. These events occurred within several days and up to several months after initiating capecitabine tablets and, in a few cases, within 1 month after stopping capecitabine tablets. These events occurred in patients with and without liver metastases.

Monitor INR more frequently and adjust the dose of the vitamin K antagonist as appropriate *[see Drug Interactions (7.2)]*.

1 INDICATIONS AND USAGE

1.1 Colorectal Cancer

Capecitabine tablets are indicated for the:
- 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.

1.2 Breast Cancer

Capecitabine tablets are indicated for the:
- 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.

1.3 Gastric, Esophageal, or Gastroesophageal Junction Cancer

Capecitabine tablets are indicated for the:
- 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.

1.4 Pancreatic Cancer

Capecitabine tablets are indicated for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen.

2 DOSAGE AND ADMINISTRATION

2. 1 Recommended Dosage for Colorectal Cancer

Adjuvant Treatment of Colon Cancer

Single Agent

The recommended dosage of capecitabine tablet is 1,250 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-Containing Regimens

The recommended dosage of capecitabine tablet is 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.

Refer to the oxaliplatin prescribing information for additional dosing information as appropriate.

Perioperative Treatment of Rectal Cancer

The recommended dosage of capecitabine is 825 mg/m^2 orally twice daily when administered with concomitant radiation therapy and 1,250 mg/m^2 orally twice daily when administered without radiation therapy as part of a peri-operative combination regimen.

Unresectable or Metastatic Colorectal Cancer

Single Agent

The recommended dosage of capecitabine tablet is 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 Oxaliplatin

The recommended dosage of capecitabine tablet is 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.

Refer to the Prescribing Information for oxaliplatin for additional dosing information as appropriate.

2.2 Recommended Dosage for Breast Cancer

Advanced or Metastatic Breast Cancer

Single Agent

The recommended dosage of capecitabine tablet is 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.
Individualize the dose and dosing schedule of capecitabine tablets based on patient risk factors and adverse reactions.

In Combination with Docetaxel

The recommended dosage of capecitabine tablet is 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 75 mg/m^2 administered intravenously on day 1 of each cycle.

Refer to the Prescribing Information for docetaxel for additional dosing information as appropriate.

2.3 Recommended Dosage for Gastric, Esophageal, or Gastroesophageal Junction Cancer

The recommended dosage of capecitabine tablets for unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer is:

- 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. Individualize the dose and dosing schedule of capecitabine tablets based on patient risk factors and adverse reactions.

The recommended dosage of capecitabine tablets for HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma is 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.

Refer to the Prescribing Information for agents used in combination for additional dosing information as appropriate.

2.4 Recommended Dosage for Pancreatic Cancer

The recommended dosage of capecitabine tablet is 830 mg/m^2 orally twice daily for the first 21 days of each 28-day cycle until disease progression, unacceptable toxicity, or for a maximum 6 cycles in combination with gemcitabine 1,000 mg/m^2 administered intravenously on days 1, 8, and 15 of each cycle.

Refer to Prescribing Information for gemcitabine for additional dosing information as appropriate.

2.5 Dosage Modifications for Adverse Reactions

Monitor patients for adverse reactions and modify dosages of capecitabine tablets as described in Table 1. Do not replace missed doses of capecitabine tablets; instead resume capecitabine tablets with the next planned dosage.

When capecitabine tablets are administered with docetaxel, withhold capecitabine tablets and docetaxel until the requirements for resuming both capecitabine tablets and docetaxel are met. Refer to the Prescribing Information for docetaxel for additional dosing information as appropriate.

Table 1 Recommended Dosage Modifications for Adverse Reactions

Severity	**Dosage Modification**	**Resume at Same or Reduced Dose (Percent of Current Dose)**
Grade 2		
1st appearance	Withhold until resolved to grade 0 to 1.	100%
2nd appearance		75%
3rd appearance		50%
4th appearance	Permanently discontinue.	-
Grade 3		
1st appearance	Withhold until resolved to grade 0 to 1.	75%
2nd appearance		50%
3rd appearance	Permanently discontinue.	-
Grade 4		
1st appearance	Permanently discontinue OR Withhold until resolved to grade 0 to 1.	50%

Hyperbilirubinemia

Patients with Grade 3 to 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 *[see Warnings and Precautions (5.10)]*.

2.6 Dosage Modification For Renal Impairment

Reduce the dose of capecitabine tablets 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) *[see Use in Specific Populations (8.6)]*.

2.7 Administration

Round the recommended dosage for patients to the nearest 150 mg dose to provide whole capecitabine tablets.

Swallow capecitabine tablets whole with water within 30 minutes after a meal. Do not chew, cut, or crush capecitabine tablets *[see Warnings and Precautions (5.12)]*.

Take capecitabine tablets 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 tablets are a hazardous drug. Follow applicable special handling and disposal procedures.[1]

3 DOSAGE FORMS AND STRENGTHS

Tablets, film-coated:

- 150 mg: Light Peach color, oval shaped with 'A015' on the one side and '150' on the other side
- 500 mg: Light Peach color, oval shaped with 'A016' on the one side and '500' on the other side

4 CONTRAINDICATIONS

Capecitabine tablets are contraindicated in patients with history of severe hypersensitivity reaction to fluorouracil or capecitabine *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Bleeding With Concomitant Use of Vitamin K Antagonists

Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine tablets concomitantly with vitamin K antagonists, such as warfarin.

Clinically significant increases in PT and INR have been reported in patients who were on stable doses of oral vitamin K antagonists at the time capecitabine tablets was introduced. These events occurred within several days and up to several months after initiating capecitabine tablets and, in a few cases, within 1 month after stopping capecitabine tablets. These events occurred in patients with and without liver metastases.

Monitor INR more frequently and adjust the dose of the vitamin K antagonist as appropriate *[see Drug Interactions (7.1)]*.

5.2 Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency

Patients with certain homozygous or compound heterozygous variants in the *DPYD* gene known to result in complete or near complete absence of DPD activity (complete DPD deficiency) are at increased risk for acute early-onset toxicity and serious, including fatal, adverse reactions due to capecitabine tablets (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity (partial DPD deficiency) may also have increased risk of serious, including fatal, adverse reactions.

Capecitabine tablets are 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 tablets 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. No capecitabine tablets dose has been proven safe for patients with complete DPD deficiency. There are insufficient data to recommend a specific dose in patients with partial DPD deficiency.

Consider testing for genetic variants of *DPYD* prior to initiating capecitabine tablets to reduce the risk of serious adverse reactions if the patient's clinical status permits and based on clinical judgement *[see Clinical Pharmacology (12.5)]*. Serious adverse reactions may still occur even if no *DPYD* variants are identified.

An FDA-authorized test for the detection of genetic variants of *DPYD* to identify patients at risk of serious adverse reactions due to increased systemic exposure to capecitabine tablets are not currently available. Currently available tests used to identify *DPYD* variants may vary in accuracy and design (e.g., which *DPYD* variant(s) they identify).

5.3 Cardiotoxicity

Cardiotoxicity can occur with capecitabine tablets. Myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy have been reported with capecitabine tablets. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

Withhold capecitabine tablets for cardiotoxicity as appropriate *[see Dosage and Administration (2.5)]*. The safety of resumption of capecitabine tablets in patients with cardiotoxicity that has resolved have not been established.

5.4 Diarrhea

Diarrhea, sometimes severe, can occur with capecitabine tablets. In 875 patients with metastatic breast or colorectal cancer who received capecitabine tablets 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 tablets and then resume at same or reduced dose or permanently discontinue based on severity and occurrence *[see Dosage and Administration (2.5)]*.

5.5 Dehydration

Dehydration can occur with capecitabine tablets. Patients with anorexia, asthenia, nausea, vomiting, or diarrhea may be at an increased risk of developing dehydration with capecitabine tablets. Optimize hydration before starting capecitabine tablets. Monitor hydration status and kidney function at baseline and as clinically indicated. Withhold capecitabine tablets and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence *[see Dosage and Administration (2.5)]*.

5.6 Renal Toxicity

Serious renal failure, sometimes fatal, can occur with capecitabine tablets. Renal impairment or coadministration of capecitabine tablets with other products known to cause renal toxicity may increase the risk of renal toxicity *[see Drug Interactions (7.3)]*.

Monitor renal function at baseline and as clinically indicated. Optimize hydration before starting capecitabine tablets. Withhold capecitabine tablets and then resume at same or reduced dose, or permanently discontinue, based on severity and occurrence *[see Dosage and Administration (2.5)]*.

5.7 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 tablets *[see Adverse Reactions (6.2)]*.

Monitor for new or worsening serious skin reactions. Permanently discontinue capecitabine tablets for severe cutaneous adverse reactions.

5.8 Palmar-Plantar Erythrodysesthesia Syndrome

Palmar-plantar erythrodysesthesia syndrome (PPES) can occur with capecitabine tablets.

In patients with metastatic breast or colorectal cancer who received capecitabine tablets 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 tablets and then resume at same or reduced dose or permanently discontinue based on severity and occurrence *[see Dosage and Administration (2.5)]*.

5.9 Myelosuppression

Myelosuppression can occur with capecitabine tablets.

In the 875 patients with metastatic breast or colorectal cancer who received capecitabine tablets as a single agent, 3.2% had grade 3 or 4 neutropenia, 1.7% had grade 3 or 4 thrombocytopenia, and 2.4% had grade 3 or 4 anemia.

In the 251 patients with metastatic breast cancer who received capecitabine tablets with docetaxel, 68% had grade 3 or 4 neutropenia, 2.8% had grade 3 or 4 thrombocytopenia, and 10% had grade 3 or 4 anemia.

Necrotizing enterocolitis (typhlitis) has been reported. Consider typhlitis in patients with fever, neutropenia and abdominal pain.

Monitor complete blood count at baseline and before each cycle. Capecitabine tablets are 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 tablets and then resume at same or reduced dose, or permanently discontinue, based on occurrence *[see Dosage and Administration (2.5)]*.

5.10 Hyperbilirubinemia

Hyperbilirubinemia can occur with capecitabine tablets. In the 875 patients with metastatic breast or colorectal cancer who received capecitabine tablets as a single agent, grade 3 hyperbilirubinemia occurred in 15% of patients and grade 4 hyperbilirubinemia occurred in 3.9%. Of the 566 patients who had hepatic metastases at baseline and the 309 patients without hepatic metastases at baseline, grade 3 or 4 hyperbilirubinemia occurred in 23% and 12%, respectively. Of these 167 patients with grade 3 or 4 hyperbilirubinemia, 19% had postbaseline increased alkaline phosphatase and 28% had postbaseline increased transaminases at any time (not necessarily concurrent). The majority of these patients with increased transaminases or alkaline phosphatase had liver metastases at baseline. In addition, 58% and 35% of the 167 patients with grade 3 or 4 hyperbilirubinemia had pre- and postbaseline increased alkaline phosphatase or transaminases (grades 1 to 4), respectively. Only 8% (n=13) and 3% (n=5) had grade 3 or 4 increased alkaline phosphatase or transaminases.

In the 596 patients who received capecitabine tablets for metastatic colorectal cancer, the incidence of grade 3 or 4 hyperbilirubinemia was similar to that observed for the pooled population of patients with metastatic breast and colorectal cancer. The median time to onset for grade 3 or 4 hyperbilirubinemia was 64 days and median total bilirubin increased from 8 µm/L at baseline to 13 µm/L during treatment with capecitabine tablets. Of the 136 patients with grade 3 or 4 hyperbilirubinemia, 49 patients had grade 3 or 4 hyperbilirubinemia as their last measured value, of which 46 had liver metastases at baseline.

In the 251 patients with metastatic breast cancer who received capecitabine tablets with docetaxel, grade 3 hyperbilirubinemia occurred in 7% and

grade 4 hyperbilirubinemia occurred in 2%.

Withhold capecitabine tablets and then resume at a same or reduced dose, or permanently discontinue, based on occurrence *[see Dosage and Administration (2.5)]*. Patients with Grade 3 to 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 *[see Dosage and Administration (2.5)]*.

5.11 Embryo-Fetal Toxicity

Based on findings from animal reproduction studies and its mechanism of action, capecitabine tablets can cause fetal harm when administered to a pregnant woman. Insufficient data is available on capecitabine tablets use in pregnant women to evaluate a drug-associated risk. In animal reproduction studies, administration of capecitabine to pregnant animals during the period of organogenesis caused embryolethality and teratogenicity in mice and embryolethality in monkeys at 0.2 and 0.6 times the human exposure (AUC) in patients who received a dosage of 1,250 mg/m^2 twice daily, respectively.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with capecitabine tablets and for 6 months following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with capecitabine tablets and for 3 months following the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.12 Eye Irritation, Skin Rash and Other Adverse Reactions from Exposure to Crushed Tablets

In instances of exposure to crushed capecitabine tablets, the following adverse reactions have been reported: eye irritation and swelling, skin rash, diarrhea, paresthesia, headache, gastric irritation, vomiting and nausea. Advise patients not to cut or crush tablets.

If capecitabine tablets must be cut or crushed, this should be done by a professional trained in safe handling of cytotoxic drugs using appropriate equipment and safety procedures *[see Dosage and Administration (2.7)]*. The safety and effectiveness have not been established for the administration of crushed capecitabine tablets.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Cardiotoxicity *[see Warnings and Precautions (5.3)]*
- Diarrhea *[see Warnings and Precautions (5.4)]*
- Dehydration *[see Warnings and Precautions (5.5)]*
- Renal Toxicity *[see Warnings and Precautions (5.6)]*
- Serious Skin Toxicities *[see Warnings and Precautions (5.7)]*
- Palmar-Plantar Erythrodysesthesia Syndrome *[see Warnings and Precautions (5.8)]*
- Myelosuppression *[see Warnings and Precautions (5.9)]*
- Hyperbilirubinemia *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Treatment of Colon Cancer

Single Agent

The safety of capecitabine tablets as a single agent was evaluated in patients with Stage III colon cancer in X-ACT *[see Clinical Studies (14.1)]*. Patients received capecitabine tablets 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle (N=995) or leucovorin 20 mg/m^2 intravenously followed by fluorouracil 425 mg/m^2 as an intravenous bolus on days 1 to 5 of each 28-day cycle (N=974). Among patients who received capecitabine tablets, the median duration of treatment was 5.4 months.

Deaths due to all causes occurred in 0.8% of patients who received capecitabine tablets on study or within 28 days of receiving study drug. Permanent discontinuation due to an adverse reaction occurred in 11% of patients who received capecitabine tablets.

Most common adverse reactions (>30%) were palmar-plantar erythrodysesthesia syndrome, diarrhea, and nausea.

Tables 2 and 3 summarize the adverse reactions and laboratory abnormalities in X-ACT.

Table 2 Adverse Reactions (≥10%) in Patients Who Received Capecitabine Tablets for Adjuvant Treatment of Colon Cancer in X-ACT

Adverse Reaction	Capecitabine Tablets (N=995)		Fluorouracil + Leucovorin (N=974)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	60	17	9	<1
Gastrointestinal				
Diarrhea	47	12	65	14
Nausea	34	2	47	2
Stomatitis	22	2	60	14
Vomiting	15	2	21	2
Abdominal pain	14	3	16	2
General				
Fatigue	16	<1	16	1
Asthenia	10	<1	10	1
Lethargy	10	<1	9	<1

Clinically relevant adverse reactions in <10% of patients are presented below:

Eye: conjunctivitis

Gastrointestinal: constipation, upper abdominal pain, dyspepsia

General: pyrexia

Metabolism and Nutrition: anorexia

Nervous System: dizziness, dysgeusia, headache

Skin & Subcutaneous Tissue: rash, alopecia, erythema

Table 3 Grade 3 or 4 Laboratory Abnormalities (>1%) in Patients Who Received Capecitabine Tablets as a Single Agent for Adjuvant Treatment of Colon Cancer in X- ACT

Laboratory Abnormality	Capecitabine Tablets (N=995)	Fluorouracil + Leucovorin (N=974)
	Grade 3 or 4 (%)	Grade 3 or 4 (%)
Bilirubin increased	20	6
Lymphocytes decreased	13	13
Neutrophils/granulocytes decreased	2.4	26
Calcium decreased	2.3	2.2
Neutrophils decreased	2.2	26
ALT increased	1.6	0.6
Calcium increased	1.1	0.7
Hemoglobin decreased	1	1.2
Platelets decreased	1	0.7

In Combination with Oxaliplatin-Containing Regimens

The safety of capecitabine tablets for the perioperative treatment of adults with Stage III colon cancer as a component of a combination chemotherapy regimen was derived from published literature *[see Clinical Studies (14.1)]*. The safety of capecitabine tablets for the adjuvant treatment of patients with Stage III colon cancer as a component of a combination chemotherapy regimen was similar to those in patients treated with capecitabine tablets as a single agent, with the exception of an increased incidence of neurosensory toxicity.

Perioperative Treatment of Rectal Cancer

The safety of capecitabine tablets for the perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy was derived from published literature *[see Clinical Studies (14.1)]*. The safety of capecitabine tablets for the perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy was similar to those in patients treated with capecitabine tablets as a single agent, with the exception of an increased incidence of diarrhea.

Metastatic Colorectal Cancer

Single Agent

The safety of capecitabine tablets as a single agent was evaluated in a pooled metastatic colorectal cancer population (Study SO14695 and Study SO14796) *[see Clinical Studies (14.1)]*. Patients received capecitabine tablets 1,250 mg/m^2 orally twice a day for the first 14 days of a 21-day cycle (N=596) or leucovorin 20 mg/m^2 intravenously followed by fluorouracil 425 mg/m^2 as an intravenous bolus on days 1 to 5 of each 28-day cycle (N=593). Among the patients who received capecitabine tablets, the median duration of treatment was 4.6 months.

Deaths due to all causes occurred in 8% of patients who received capecitabine tablets on study or within 28 days of receiving study drug. Permanent discontinuation due to an adverse reaction or intercurrent illness occurred in 13% of patients who received capecitabine tablets.

Most common adverse reactions (>30%) were anemia, diarrhea, palmar-plantar erythrodysesthesia syndrome, hyperbilirubinemia, nausea, fatigue, and abdominal pain.

Table 4 shows the adverse reactions occurring in this pooled colorectal cancer population.

Table 4 Adverse Reactions (≥10%) in Patients Who Received Capecitabine Tablets in Pooled Metastatic Colorectal Cancer Population (Study SO14695 and Study SO14796)

Adverse Reaction	Capecitabine Tablets (N=596)			Fluorouracil + Leucovorin (N=593)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Blood and Lymphatic System						
Anemia	80	2	<1	79	1	<1
Neutropenia	13	1	2	46	8	13
Gastrointestinal						
Diarrhea	55	13	2	61	10	2
Nausea	43	4	–	51	3	<1
Abdominal pain	35	9	<1	31	5	–
Vomiting	27	4	<1	30	4	<1
Stomatitis	25	2	<1	62	14	1
Constipation	14	1	<1	17	1	–
Gastrointestinal motility disorder	10	<1	–	7	<1	–
Oral discomfort	10	–	–	10	–	–
Skin and Subcutaneous Tissue						
Palmar-plantar erythrodysesthesia syndrome	54	17	NA	6	1	NA
Dermatitis	27	1	–	26	1	–
Hepatobiliary						
Hyperbilirubinemia	48	18	5	17	3	3
General						
Fatigue*	42	4	–	46	4	–
Pyrexia	18	1	–	21	2	–
Edema	15	1	–	9	1	–
Pain	12	1	–	10	1	–
Metabolism and Nutrition						
Decreased appetite	26	3	<1	31	2	<1
Respiratory Thoracic and Mediastinal						
Dyspnea	14	1	–	10	<1	1
Eye						
Eye irritation	13	–	–	10	<1	–
Nervous System						
Peripheral sensory neuropathy	10	–	–	4	–	–
Headache	10	1	–	7	–	–
Musculoskeletal						
Back pain	10	2	–	9	<1	–

– Not observed

*Includes weakness

NA = Not Applicable

Clinically relevant adverse reactions in <10% of patients are presented below:

Eye: abnormal vision

Gastrointestinal: upper gastrointestinal tract inflammatory disorders, gastrointestinal hemorrhage, ileus

General: chest pain

Infections: viral

Metabolism and Nutrition: dehydration

Musculoskeletal: arthralgia

Nervous System: dizziness (excluding vertigo), insomnia, taste disturbance

Psychiatric: mood alteration, depression

Respiratory, Thoracic, and Mediastinal: cough, pharyngeal disorder

Skin and Subcutaneous Tissue: skin discoloration, alopecia

Vascular: venous thrombosis

In Combination with Oxaliplatin

The safety of capecitabine tablets for the treatment of patients with unresectable or metastatic colorectal cancer as a component of a combination chemotherapy regimen was derived from published literature *[see Clinical Studies (14.1)]*. The safety of capecitabine tablets for the treatment of patients with unresectable or metastatic colorectal cancer as a component of a combination chemotherapy regimen was similar to those in patients treated with capecitabine tablets as a single agent, with the exception of an increased incidence of peripheral neuropathy.

Metastatic Breast Cancer

In Combination with Docetaxel

The safety of capecitabine tablets in combination with docetaxel was evaluated in patients with metastatic breast cancer in Study SO14999 *[see Clinical Studies (14.2)]*. Patients received capecitabine tablets 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle with docetaxel 75 mg/m^2 as 1- hour intravenous infusion on day 1 of each 21-day cycle for at least 6 weeks or docetaxel 100 mg/m^2 as a 1-hour intravenous infusion on day 1 of each 21-day cycle for at least 6 weeks. Among patients who received capecitabine tablets, the mean duration of treatment was 4.2 months.

Permanent discontinuation due to an adverse reaction occurred in 26% of patients who received capecitabine tablets. Dosage interruptions due to an adverse reaction occurred in 79% of patients who received capecitabine tablets and dosage reductions due to an adverse reaction occurred in 65%.

Most common adverse reactions (>30%) were diarrhea, stomatitis, palmar-plantar erythrodysesthesia syndrome, nausea, alopecia, vomiting, edema, and abdominal pain.

Table 5 summarizes the adverse reactions in Study SO14999.

Table 5 Adverse Reactions (≥10%) in Patients Who Received Capecitabine Tablets with Docetaxel for Metastatic Breast Cancer in Study SO14999

Adverse Reaction	Capecitabine Tablets with Docetaxel (N=251)			Docetaxel (N=255)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal						
Diarrhea	67	14	<1	48	5	<1
Stomatitis	67	17	<1	43	5	–
Nausea	45	7	–	36	2	–
Vomiting	35	4	1	24	2	–
Abdominal pain	30	3	<1	24	2	–
Constipation	20	2	–	18	–	–
Dyspepsia	14	–	–	8	1	–
Skin and Subcutaneous Tissue						
Palmar-plantar erythrodysesthesia syndrome	63	24	NA	8	1	NA
Alopecia	41	6	–	42	7	–
Nail disorder	14	2	–	15	–	–
Cardiac						
Edema	33	<2	–	34	<3	1
General						
Pyrexia	28	2	–	34	2	–
Asthenia	26	4	<1	25	6	–
Fatigue	22	4	–	27	6	–
Weakness	16	2	–	11	2	–

Pain in Limb	13	<1	–	13	2	–
Blood and Lymphatic System						
Neutropenic fever	16	3	13	21	5	16
Nervous System						
Taste disturbance	16	<1	–	14	<1	–
Headache	15	3	–	15	2	–
Paresthesia	12	<1	–	16	1	–
Dizziness	12	–	–	8	<1	–
Musculoskeletal and Connective Tissue						
Arthralgia	15	2	–	24	3	–
Myalgia	15	2	–	25	2	–
Back Pain	12	<1	–	11	3	–
Respiratory, Thoracic and Mediastinal						
Dyspnea	14	2	<1	16	2	–
Cough	13	1	–	22	<1	–
Sore Throat	12	2	–	11	<1	–
Metabolism and Nutrition						
Anorexia	13	<1	–	11	<1	–
Appetite decreased	10	–	–	5	–	–
Dehydration	10	2	–	7	<1	<1
Eye						
Lacrimation increased	12	–	–	7	<1	–

– Not observed

NA = Not Applicable

Clinically relevant adverse reactions in <10% of patients are presented below:

Blood and Lymphatic System: agranulocytosis, prothrombin decreased

Cardiac: supraventricular tachycardia

Eye: conjunctivitis, eye irritation

Gastrointestinal: ileus, necrotizing enterocolitis, esophageal ulcer, hemorrhagic diarrhea, dry mouth

General: chest pain (non-cardiac), lethargy, pain, influenza-like illness

Hepatobiliary: jaundice, abnormal liver function tests, hepatic failure, hepatic coma, hepatotoxicity

Immune System: hypersensitivity

Infection: hypoesthesia, neutropenic sepsis, sepsis, bronchopneumonia, oral candidiasis, urinary tract infection

Metabolism and Nutrition: weight decreased

Musculoskeletal and Connective Tissue: bone pain

Nervous System: insomnia, peripheral neuropathy, ataxia, syncope, taste loss, polyneuropathy, migraine

Psychiatric: depression

Renal and Urinary: renal failure

Respiratory, Thoracic and Mediastinal: upper respiratory tract infection, pleural effusion, epistaxis, rhinorrhea

Skin and Subcutaneous Tissue: pruritis, rash erythematous, dermatitis, nail discoloration, onycholysis

Vascular: lymphedema, hypotension, venous phlebitis and thrombophlebitis, postural hypotension, flushing

Table 6 summarizes the laboratory abnormalities in this trial.

Table 6 Laboratory Abnormalities (≥20%) in Patients Who Received Capecitabine Tablets with Docetaxel for Metastatic Breast Cancer in Study SO14999

	Capecitabine Tablets with Docetaxel (N=251)			Docetaxel (N=255)		
Laboratory Abnormality	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematologic						
Lymphocytopenia	99	48	41	98	44	40
Leukopenia	91	37	24	88	42	33
Neutropenia	86	20	49	87	10	66
Anemia	80	7	3	83	5	<1
Thrombocytopenia	41	2	1	23	1	2
Hepatobiliary						
Hyperbilirubinemia	20	7	2	6	2	2

Single Agent

The safety of capecitabine tablets as a single agent was evaluated in patients with metastatic breast cancer in Study SO14697 *[see Clinical Studies (14.2)]*. Patients received capecitabine tablets 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle. The mean duration of treatment was 3.7 months.

Permanent discontinuation due to an adverse reaction or intercurrent illness occurred in 8% of patients.

Most common adverse reactions (>30%) were lymphopenia, anemia, diarrhea, hand-and-foot syndrome, nausea, fatigue, vomiting, and dermatitis.

Table 7 summarizes the adverse reactions in Study SO14697.

Table 7 Adverse Reactions (>10%) in Patients Who Received Capecitabine Tablets for Metastatic Breast Cancer in Study SO14697

	Capecitabine Tablets (n=162)		
Adverse Reaction	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Blood and Lymphatic System			
Lymphopenia	94	44	15
Anemia	72	3	1
Neutropenia	26	2	2
Thrombocytopenia	24	3	1
Gastrointestinal			
Diarrhea	57	12	3
Nausea	53	4	–
Vomiting	37	4	–
Stomatitis	24	7	–
Abdominal pain	20	4	–
Constipation	15	1	–
Skin and Subcutaneous Tissue			
Hand-and-foot syndrome	57	11	NA
Dermatitis	37	1	–
General			
Fatigue	41	8	–
Pyrexia	12	1	–
Metabolism and Nutrition			
Anorexia	23	3	–
Hepatobiliary			
Hyperbilirubinemia	22	9	2
Nervous System			
Paresthesia	21	1	–
Eye			
Eye irritation	15	–	–

– = Not observed

NA = Not Applicable

Pooled Safety Population

Clinically relevant adverse reactions in <10% of patients who received capecitabine tablets as a single agent are presented below.

Blood & Lymphatic System: leukopenia, coagulation disorder, bone marrow depression, pancytopenia

Cardiac: tachycardia, bradycardia, atrial fibrillation, myocarditis, edema

Ear: vertigo

Eye: conjunctivitis

Gastrointestinal: abdominal distension, dysphagia, proctalgia, gastric ulcer, ileus, gastroenteritis, dyspepsia

General: chest pain, influenza-like illness, hot flushes, pain, thirst, fibrosis, hemorrhage, edema, pain in limb

Hepatobiliary: hepatic fibrosis, hepatitis, cholestatic hepatitis, abnormal liver function tests

Immune System: drug hypersensitivity

Infections: bronchitis, pneumonia, keratoconjunctivitis, sepsis, fungal infections

Metabolism and Nutrition: cachexia, hypertriglyceridemia, hypokalemia, hypomagnesemia, dehydration

Musculoskeletal and Connective Tissue: myalgia, arthritis, muscle weakness

Nervous System: insomnia, ataxia, tremor, dysphasia, encephalopathy, dysarthria, impaired balance, headache, dizziness

Psychiatric: depression, confusion

Renal and Urinary: renal impairment

Respiratory, Mediastinal and Thoracic: cough, epistaxis, respiratory distress, dyspnea

Skin and Subcutaneous Tissue: nail disorder, sweating increased, photosensitivity reaction, skin ulceration, pruritus, radiation recall syndrome

Vascular: hypotension, hypertension, lymphedema, pulmonary embolism

Unresectable or Metastatic Gastric, Esophageal, or Gastroesophageal Junction Cancer

-
The safety of capecitabine tablets for the treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen was derived from published literature *[see Clinical Studies (14.3)]*. The safety of capecitabine tablets for the treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen was consistent with the known safety profile of capecitabine tablets.

The safety of capecitabine tablets for the treatment of patients 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 was derived from the published literature *[see Clinical Studies (14.3)]*. The safety of capecitabine tablets for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma was consistent with the known safety profile of capecitabine tablets.

-
Pancreatic Cancer

The safety of capecitabine tablets for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen was derived from the published literature *[see Clinical Studies (14.4)]*. The safety of capecitabine tablets for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen was consistent with the known safety profile of capecitabine tablets.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of capecitabine tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye: lacrimal duct stenosis, corneal disorders including keratitis

Hepatobiliary: hepatic failure

Immune System Disorders: angioedema

Nervous System: toxic leukoencephalopathy

Renal & Urinary: acute renal failure secondary to dehydration including fatal outcome

Skin & Subcutaneous Tissue: cutaneous lupus erythematosus, severe skin reactions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN), persistent or severe PPES can eventually lead to loss of fingerprints

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Capecitabine Tablets

Allopurinol

Concomitant use with allopurinol may decrease concentration of capecitabine's active metabolites *[see Clinical Pharmacology (12.3)]*, which may decrease efficacy. Avoid concomitant use of allopurinol with capecitabine tablets.

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.

7.2 Effect of Capecitabine Tablets on Other Drugs

CYP2C9 Substrates

Capecitabine tablets increased exposure of CYP2C9 substrates *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions related to these substrates. Closely monitor for adverse reactions of CYP2C9 substrates where minimal concentration changes may lead to serious adverse reactions when used concomitantly with capecitabine tablets (e.g., anticoagulants, antidiabetic drugs).

Vitamin K Antagonists

Capecitabine tablets increases exposure of vitamin K antagonist *[see Clinical Pharmacology (12.3)]*, which may alter coagulation parameters and/or bleeding and could result in death *[see Warning and Precautions (5.1)]*. These events may occur within days of treatment initiation and up to 1 month after discontinuation of capecitabine tablets.

Monitor INR more frequently and refer to the prescribing information of oral vitamin K antagonist for dosage adjustment, as appropriate, when capecitabine tablets are used concomitantly with vitamin K antagonist.

Phenytoin

Capecitabine tablets may increases 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 dosage adjustment, as appropriate, when capecitabine tablets are used concomitantly with phenytoin.

7.3 Nephrotoxic Drugs

Due of the additive pharmacologic effect, concomitant use of capecitabine tablets with other drugs known to cause renal toxicity may increase the risk of renal toxicity *[see Warnings and Precautions (5.6)]*. Closely monitor for signs of renal toxicity when capecitabine tablets are used concomitantly with nephrotoxic drugs (e.g. platinum salts, irinotecan, methotrexate, intravenous bisphosphonates).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, capecitabine tablets can cause fetal harm when administered to a pregnant woman. Available human data with capecitabine tablets use in pregnant women is not sufficient to inform the drug-associated risk. In animal reproduction studies, administration of capecitabine to pregnant animals during the period of organogenesis caused embryolethality and teratogenicity in mice and embryolethality in monkeys at 0.2 and 0.6 times the exposure (AUC) in patients receiving the recommended dose of 1,250 mg/m^2 twice daily, respectively *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Oral administration of capecitabine to pregnant mice during the period of organogenesis at a dose of 198 mg/kg/day caused malformations and embryo lethality. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values that were approximately 0.2 times the AUC values in patients administered the recommended daily dose. Malformations in mice included cleft palate, anophthalmia, microphthalmia, oligodactyly, polydactyly, syndactyly, kinky tail and dilation of cerebral ventricles. Oral administration of capecitabine to pregnant monkeys during the period of organogenesis at a dose of 90 mg/kg/day, caused fetal lethality.

This dose produced 5′-DFUR AUC values that were approximately 0.6 times the AUC values in patients administered the recommended daily dose.

8.2 Lactation

Risk Summary

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. Capecitabine metabolites were present in the milk of lactating mice *(see Data)*. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with capecitabine tablets and for 1 week after the last dose.

Data

Lactating mice given a single oral dose of capecitabine excreted significant amounts of capecitabine metabolites into the milk.

8.3 Females and Males of Reproductive Potential

Capecitabine tablets can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating capecitabine tablets.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with capecitabine tablets and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with capecitabine tablets and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Based on animal studies, capecitabine tablets may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of capecitabine tablets in pediatric patients have not been established.

Safety and effectiveness were assessed, but not established in two single arm studies in 56 pediatric patients aged 3 months to <17 years with newly diagnosed gliomas. In both trials, pediatric patients received an investigational pediatric formulation of capecitabine concomitantly with and following completion of radiation therapy (total dose of 5,580 cGy in 180 cGy fractions). The relative bioavailability of the investigational formulation to capecitabine tablets was similar.

The adverse reaction profile was consistent with that of adults, with the exception of laboratory abnormalities which occurred more commonly in pediatric patients. The most frequently reported laboratory abnormalities (per-patient incidence ≥ 40%) were increased ALT (75%), lymphocytopenia (73%), hypokalemia (68%), thrombocytopenia (57%), hypoalbuminemia (55%), neutropenia (50%), low hematocrit (50%), hypocalcemia (48%), hypophosphatemia (45%) and hyponatremia (45%).

8.5 Geriatric Use

Of 7,938 patients with colorectal cancer who were treated with capecitabine tablets, 33% were older than 65 years. Of the 4,536 patients with metastatic breast cancer who were treated with capecitabine tablets, 18% were older than 65 years.

Of 1,951 patients with gastric, esophageal, or gastrointestinal junction cancer who were treated with capecitabine tablets, 26% were older than 65 years.

Of 364 patients with pancreatic cancer who received adjuvant treatment with capecitabine tablets, 47% were 65 years or older.

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 capecitabine tablets compared to younger patients. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil *[see Drug Interactions (7.1)]*.

8.6 Renal Impairment

The exposure of capecitabine and its inactive metabolites (5-DFUR and FBAL) increases in patients with CLcr <50 mL/min as determined by Cockcroft-Gault *[see Clinical Pharmacology (12.3)]*. Reduce the dosage for patients with CLcr of 30 to 50 mL/min *[see Dosage and Administration (2.6)]*. There is limited experience with capecitabine tablets in patients with CLcr <30 mL/min, and a dosage has not been established in those patients. If no treatment alternative exists, capecitabine tablets could be administered to such patients on an individual basis applying a reduced starting dose, close monitoring of a patient's clinical and biochemical data and dose modifications guided by observed adverse reactions.

8.7 Hepatic Impairment

The exposure of capecitabine increases in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the safety and pharmacokinetics of capecitabine tablets are unknown *[see Clinical Pharmacology (12.3)]*. Monitor patients with hepatic impairment more frequently for adverse reactions.

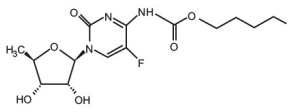
10 OVERDOSAGE

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

Although no clinical experience using dialysis as a treatment for capecitabine tablets 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.

11 DESCRIPTION

Capecitabine, USP is a nucleoside metabolic inhibitor. The chemical name is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl]-cytidine and has a molecular formula of $C_{15}H_{22}FN_3O_6$ and a molecular weight of 359.35. Capecitabine has the following structural formula:



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

Capecitabine tablets, USP are supplied as oval shaped film-coated tablets for oral use. Each light peach colored tablet contains 150 mg capecitabine, USP and each light peach colored tablet contains 500 mg capecitabine, USP. The inactive ingredients in capecitabine tablets include: anhydrous lactose, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, and purified water. The light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, iron oxide yellow and iron oxide red.

12 CLINICAL PHARMACOLOGY

12.1 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, $N^{5\text{-}10}$-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.

12.2 Pharmacodynamics

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

12.3 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/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
tablets 1,255 mg/m^2 orally twice daily (the recommended dosage when used as single
agent), the median T_{max} 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 C_{max} and AUC_{0-INF} of capecitabine was decreased by 60% and 34%, respectively.
The mean C_{max} and AUC_{0-INF} of fluorouracil were also decreased by 37 % and 12%,
respectively. The T_{max} 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
tablets 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 (FUH_2). The pyrimidine ring of FUH_2 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.

Specific Populations

Following therapeutic doses of capecitabine tablets, no clinically meaningful difference in
the pharmacokinetics of 5'-DFUR, fluorouracil or FBAL were observed based on sex
(202 females and 303 males) and race (455 White, 22 Black, and 28 Other). No clinically
meaningful difference on the pharmacokinetics of 5'-DFUR and fluorouracil were
observed based on
age (range: 27 to 86 years); however, the AUC of FBAL increased by 15% following a 20% increase in age.

Racial or Ethnic Groups

Following administration of capecitabine tablets 825 mg/m^2 orally twice daily for 14 days
(0.66 times the recommended dosage), the C_{max} and AUC of capecitabine decreased by
36% and 24%, respectively in Japanese patients (n=18) compared to White patients
(n=22). The C_{max} and
AUC of FBAL decreased by approximately 25% and 34%, respectively in Japanese patients compared to
White patients; however, the clinical significance of these differences is unknown.
No clinically significant differences in the pharmacokinetics of 5'-DFCR, 5'-DFUR or
fluorouracil were observed.

Patients with Renal Impairment

Table 8 Effect of Renal Impairment on the Pharmacokinetics of Capecitabine, 5'-DFUR, and FBAL

Renal Impairment[a]	**Changes in AUC[b]**			
	Capecitabine	**5'-DFUR[c]**	**FBAL[c]**	**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%
[a] Compared to patients with CLcr >80 mL/min [b] Following administration of capecitabine tablets 1,250 mg/m^2 orally twice daily; day 1 observations [c] Capecitabine metabolite CLcr= Creatine Clearance, AUC= Area under the plasma concentration-time curve				

Patients with Hepatic Impairment

AUC_{0-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-INF} and C_{max} of capecitabine increased by 60%. The effect of severe
hepatic impairment on the pharmacokinetics of capecitabine and its metabolites are
unknown.

Drug Interaction Studies

Clinical Studies

Effect of Capecitabine on Warfarin: In four patients with cancer, chronic administration
of capecitabine tablets 1,250 mg/m^2 twice daily with a single dose of warfarin 20 mg
increased the mean AUC of S-
warfarin by 57% and decreased its clearance by 37%. Baseline corrected AUC of INR in
these 4 patients increased by 2.8-fold, and the maximum observed mean INR value
was increased by 91%.

Effect of Capecitabine on Celecoxib: Concomitant administration of multiple doses
of capecitabine (capecitabine
tablets 1,000 mg/m^2 twice daily for 14 days) increased celecoxib (sensitive CYP2C9 substrate) AUC
by 28%, C_{max} by 24% and C_{trough} by 30%.

Effect of Antacids on Capecitabine: When an aluminum hydroxide-
and magnesium hydroxide- containing antacid was administered immediately after a
capecitabine tablets dose of 1,250 mg/m^2 in patients with cancer, AUC and
C_{max} increased by 16% and 35%, respectively, for capecitabine and by 18% and 22%,
respectively, for 5'-DFCR. No effect was observed on the other three major metabolites
(5'-DFUR, fluorouracil, FBAL) of capecitabine tablets.

Effect of Allopurinol on Capecitabine: Concomitant use with allopurinol may decrease conversion of
capecitabine to the active metabolites, FdUMP and FUTP.

Effect of Capecitabine on Docetaxel and Effect of Docetaxel on Capecitabine:
Capecitabine tablets had no effect on the pharmacokinetics of docetaxel (C_{max} and
AUC) and docetaxel has no effect on
the pharmacokinetics of capecitabine and the fluorouracil precursor 5'-DFUR.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Capecitabine and its metabolites (5'-DFUR, 5'-
DFCR, fluorouracil, and FBAL) did not inhibit CYP1A2, CYP2A6, CYP3A4, CYP2C19, CYP2D6, or CYP2E1 in
vitro.

12.5 Pharmacogenomics

The *DPYD* gene encodes the enzyme DPD, which is responsible for the catabolism of
>80% of fluorouracil. Approximately 3 to 5% of White populations have partial DPD

deficiency and 0.2% of White populations have complete DPD deficiency, which may be due to certain genetic
no function or decreased function variants in *DPYD* resulting in partial to complete or near complete absence of enzyme activity. DPD deficiency is estimated to be more prevalent in Black or African American populations compared to White populations. Insufficient information is available to estimate the prevalence of DPD deficiency in other populations.

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 tablets. Partial DPD deficiency can result from the presence of either two decreased function *DPYD* variants or one normal function plus either a decreased function or a no function *DPYD* variant. Patients with partial DPD deficiency may also be at an increased risk for toxicity from capecitabine tablets.

Four *DPYD* variants have been associated with impaired DPD activity in White populations, especially when present as homozygous or compound heterozygous variants: c.1905+1G>A (*DPYD* *2A), c.1679T>G (*DPYD* *13), c.2846A>T, and c.1129-5923C>G (Haplotype B3). *DPYD**2A and *DPYD**13 are no function variants, and c.2846A>T and c.1129-5923C>G are decreased function variants. The decreased function *DPYD* variant c.557A>G is observed in individuals of African ancestry. This is not a complete listing of all *DPYD* variants that may result in DPD deficiency *[see Warnings and Precautions (5.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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.

In studies of fertility and general reproductive performance in female mice, oral capecitabine doses of 760 mg/kg/day (about 2,300 mg/m^2/day) disturbed estrus and consequently caused a decrease in fertility. In mice that became pregnant, no fetuses 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 spermatocytes and spermatids. In separate pharmacokinetic studies, this dose in mice produced 5'-DFUR AUC values about 0.7 times the corresponding values in patients administered the recommended daily dose.

14 CLINICAL STUDIES

14.1 Colorectal Cancer

Adjuvant Treatment of Colon Cancer

Single Agent

The efficacy of capecitabine tablets was evaluated in X-ACT (NCT00009737), a multicenter, randomized, controlled clinical trial. Eligible patients were between 18 and 75 years of age with histologically-confirmed Dukes' Stage C colon cancer with at least one positive lymph node and to have undergone (within 8 weeks prior to randomization) complete resection of the primary tumor without macroscopic or microscopic evidence of remaining tumor. Patients were also required to have no prior cytotoxic chemotherapy or immunotherapy (except steroids) and have an ECOG performance status of 0 or 1 (KPS $\geq$70%), ANC $\geq$1.5x10^9/L, platelets $\geq$100x10^9/L, serum creatinine $\leq$1.5 ULN, total bilirubin $\leq$1.5 ULN, AST/ALT $\leq$2.5 ULN and CEA within normal limits at time of randomization.

Patients (n=1,987) were randomized to capecitabine tablets 1,250 mg/m^2 orally twice daily for the first 14 days of a 21-day cycle for a total of 8 cycles or fluorouracil 425 mg/m^2 and leucovorin 20 mg/m^2 intravenously on days 1 to 5 of each 28-day cycle for a total of 6 cycles. The capecitabine tablets dose was reduced in patients with baseline CLcr of 30 to 50 mL/min. The major efficacy outcome measure was disease-free survival (DFS).

The baseline demographics are shown in Table 9. The baseline characteristics were well-balanced between arms.

Table 9 Baseline Demographics in X-ACT

	Capecitabine Tablets (N=1,004)	**Fluorouracil + Leucovorin (N=983)**
Age (median, years)	62	63
Range	(25 to 80)	(22 to 82)
Sex		
Male, %	54	54
Female, %	46	46
ECOG Performance Status		
0, %	85	85
1, %	15	15
Staging – Primary Tumor		
PT1, %	1	0.6
PT2, %	9	9
PT3, %	76	76
PT4, %	14	0
Other, %	0.1	14
Staging – Lymph Node		
pN1, %	69	71
pN2, %	30	29
Other, %	0.4	0.1

Efficacy results are summarized in Table 10 and Figures 1 and 2. The median follow-up at the time of the analysis was 6.9 years. Because the upper 2-sided 95% confidence limit of hazard ratio for DFS was less than 1.20, capecitabine tablets was non-inferior to fluorouracil + leucovorin. The choice of the non-inferiority margin of 1.20 corresponds to the retention of approximately 75% of the fluorouracil + leucovorin effect on DFS. The hazard ratio for capecitabine tablets compared to fluorouracil + leucovorin with respect to overall survival was 0.86 (95% CI 0.74, 1.01). The 5-year overall survival rates were 71% for capecitabine tablets and 68% for fluorouracil + leucovorin.

Table 10 Efficacy Results in X-ACTa (All Randomized Population)

Efficacy Parameters	**Capecitabine Tablets (N=1,004)**	**Fluorouracil + Leucovorin (N=983)**
5-year Disease-free Survival Rate[b]	59%	55%
Hazard Ratio	0.88	
(95% CI)	(0.77, 1.01)	
p-value[c]	p = 0.068	

[a]Approximately 93.4 % had 5-year DFS information

[b] Based on Kaplan-Meier estimates

[c] Wald chi-square test

Figure 1 Kaplan-Meier Estimates of Disease-Free Survival in X-ACT (All Randomized Population)

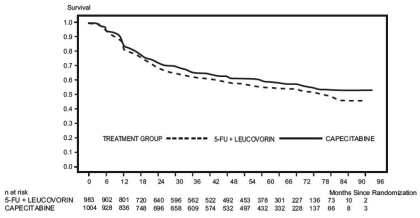
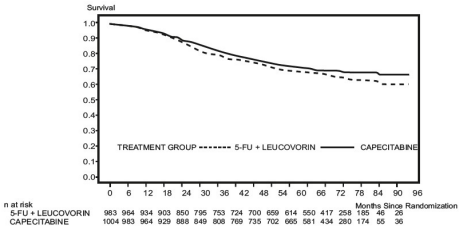


Figure 2 Kaplan-Meier Estimates of Overall Survival in X-ACT (All Randomized Population)



In Combination with Oxaliplatin-Containing Regimens

The efficacy of capecitabine tablets in combination with oxaliplatin for the adjuvant treatment of patients with Stage III colon cancer as a component of a combination chemotherapy regimen was derived from studies in the published literature, including NO16968 [NCT00069121], a multicenter, open-label, randomized trial, where the major efficacy outcome measure was disease free survival.

Perioperative Treatment of Rectal Cancer

The efficacy of capecitabine tablets for the perioperative treatment of adults with locally advanced rectal cancer as a component of chemoradiotherapy was derived from studies in the published literature, including Rektum-III [NCT01500993], a randomized, open-label, multicenter, non-inferiority trial, where the major efficacy outcome measure was overall survival.

Metastatic Colorectal Cancer

The efficacy of capecitabine tablets as a single agent was evaluated in two open-label, multicenter, randomized, controlled clinical trials (Study SO14695 and Study SO14796). Eligible patients received first-line treatment for metastatic colorectal cancer. Patients were randomized to capecitabine tablets 1,250 mg/m^2 twice daily for first 14 days of a 21-day cycle or leucovorin 20 mg/m^2 intravenously followed by fluorouracil 425 mg/m^2 as an intravenous bolus on days 1 to 5 of each 28-day cycle.

The efficacy outcome measures were overall survival, time to progression and response rate (complete plus partial responses). Responses were defined by the World Health Organization criteria and submitted to a blinded independent review committee (IRC). Differences in assessments between the investigator and IRC were reconciled by the sponsor, blinded to treatment arm, according to a specified algorithm. Survival was assessed based on a non-inferiority analysis.

The baseline demographics are shown in Table 11.

Table 11 Baseline Demographics for Study SO14695 and Study SO14796

	Study SO14695		**Study SO14796**	
	Capecitabine Tablets (N=302)	**Fluorouracil + Leucovorin (N=303)**	**Capecitabine Tablets (N=301)**	**Fluorouracil + Leucovorin (N=301)**
Age (median, years)	64	63	64	64
Range	(23 to 86)	(24 to 87)	(29 to 84)	(36 to 86)
Sex				
Male, %	60	65	57	57
Female, %	40	35	43	43
Karnofsky PS (median)	90	90	90	90
Range	(70 to 100)	(70 to 100)	(70 to 100)	(70 to 100)
Colon, %	74	77	66	65
Rectum, %	26	23	34	35
Prior radiation therapy, %	17	21	14	14
Prior adjuvant fluorouracil, %	28	36	19	14

Efficacy results for Study SO14695 and Study SO14796 are shown in Table 12 and Table 13.

Table 12 Efficacy Results for First-Line Treatment of Metastatic Colorectal Cancer (Study SO14695)

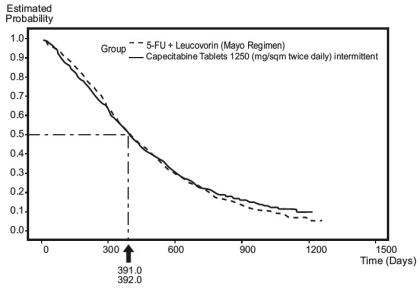
	Capecitabine Tablets (N=302)	**Fluorouracil + Leucovorin (N=303)**
Overall Response Rate		
% (95% CI)	21 (16, 26)	11 (8, 15)
p-value	0.0014	
Time to Progression		
Median, months (95% CI)	4.2 (3.9, 4.5)	4.3 (3.4, 5.0)
Hazard Ratio	0.99	
95% CI	(0.84, 1.17)	
Overall Survival		
Median, months (95% CI)	12.5 (10.5, 14.3)	13.4 (12.0, 14.7)
Hazard Ratio	1.00	
95% CI	(0.84, 1.18)	

Table 13 Efficacy Results for First-Line Treatment of Metastatic Colorectal Cancer (Study SO14796)

	Capecitabine Tablets (N=301)	**Fluorouracil + Leucovorin (N=301)**
Overall Response Rate		
% (95% CI)	21 (16, 26)	14 (10, 18)
p-value	0.027	
Time to Progression		
Median, months (95% CI)	4.5 (4.2, 5.5)	4.3 (3.4, 5.1)
Hazard Ratio	0.97	
95% CI	(0.82, 1.14)	
Overall Survival		
Median, months (95% CI)	13.3 (12.1, 14.8)	12.1 (11.1,14.1)
Hazard Ratio	0.92	
95% CI	(0.78, 1.09)	

Efficacy results of the pooled population from Study SO14695 and Study SO14796 are shown in Figure 3. Statistical analyses were performed to determine the percent of the survival effect of fluorouracil + leucovorin that was retained by capecitabine tablets. The estimate of the survival effect of fluorouracil + leucovorin was derived from a meta-analysis of ten randomized studies from the published literature comparing fluorouracil to regimens of fluorouracil + leucovorin that were similar to the control arms used in these Studies SO14695 and SO14796. The method for comparing the treatments was to examine the worst case (95% confidence upper bound) for the difference between fluorouracil + leucovorin and capecitabine tablets, and to show that loss of more than 50% of the fluorouracil + leucovorin survival effect was ruled out. It was demonstrated that the percent of the survival effect of fluorouracil + leucovorin maintained was at least 61% for Study SO14796 and 10% for Study SO14695. The pooled result is consistent with a retention of at least 50% of the effect of fluorouracil + leucovorin. It should be noted that these values for preserved effect are based on the upper bound of the fluorouracil + leucovorin vs capecitabine tablets difference.

Figure 3 Kaplan-Meier Curve for Overall Survival of Pooled Data (Studies SO14695 and SO14796)



In Combination with Oxaliplatin

The efficacy of capecitabine tablets for the treatment of patients with unresectable or metastatic colorectal cancer as a component of a combination chemotherapy regimen was derived from studies in the published literature, including NO16966 [NCT00069095], a randomized, non-inferiority, 2x2 factorial trial, where the major efficacy outcome measure was progression free survival.

14.2 Metastatic Breast Cancer

In Combination With Docetaxel

The efficacy of capecitabine tablets in combination with docetaxel was evaluated in an open-label, multicenter, randomized trial (Study SO14999). Eligible patients had metastatic breast cancer resistant to, or recurring during or after an anthracycline-containing therapy, or relapsing during or recurring within 2 years of completing an anthracycline-containing adjuvant therapy were enrolled. Patients were randomized to capecitabine tablets 1,250 mg/m^2 twice daily for the first 14 days of a 21-day cycle and docetaxel 75 mg/m^2 as a 1-hour intravenous infusion on day 1 of day of a 21- day cycle or docetaxel 100 mg/m^2 as a 1-hour intravenous infusion on day 1 of a 21-day cycle. The efficacy outcome measures were time to disease progression, overall survival, and response rate.

Patient demographics are provided in Table 14.

Table 14
Baseline Demographics in Metastatic Breast Cancer (Study SO14999)

	Capecitabine Tablets + Docetaxel (N=255)	**Docetaxel (N=256)**
Age (median, years)	52	51
Karnofsky Performance Status (median)	90	90
Site of Disease		
Lymph nodes, %	47	49
Liver, %	45	48
Bone, %	42	46
Lung, %	37	39
Skin, %	29	29
Prior Chemotherapy		
Anthracycline[1], %	100	100
Fluorouracil, %	77	74
Paclitaxel, %	10	9
Resistance to an Anthracycline		
No resistance, %	7	7
Progression on anthracycline therapy, %	26	29
Stable disease after 4 cycles of anthracycline therapy, %	16	16
Relapsed within 2 years of completion of anthracycline-adjuvant therapy, %	31	29
Experienced a brief response to anthracycline therapy, with subsequent progression while on therapy or within 12 months after last dose, %	20	20
No. of Prior Chemotherapy Regimens for Treatment of Metastatic Disease		
0, %	35	31
1, %	48	53
2, %	17	15
3, %	0	1

[1]Includes 10 patients in combination and 18 patients in single agent arms treated with an anthracenedione

Efficacy results are shown in Table 15, Figure 4 and Figure 5.

Table 15 Efficacy Results in Metastatic Breast Cancer (Study SO14999)

Efficacy Parameter	**Capecitabine Tablets + Docetaxel (N=255)**	**Docetaxel (N=256)**
Time to Disease Progression		
Median, months	6.1	4.2
95% CI	(5.4, 6.5)	(3.5, 4.5)
Hazard Ratio	0.643	
p-value	0.0001	
Overall Survival		
Median, months	14.5	11.6
95% CI	(12.3, 16.3)	(9.8, 12.7)
Hazard Ratio	0.775	
p-value	0.0126	
Response Rate[1]	32%	22%

[1] The response rate reported represents a reconciliation of the investigator and IRC assessments performed by the sponsor according to a predefined algorithm.

Figure 4 Kaplan-Meier Estimates for Time to Disease Progression in Metastatic Breast Cancer (Study SO14999)

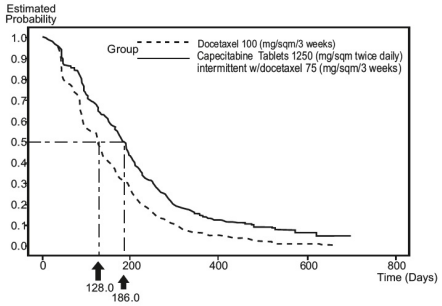
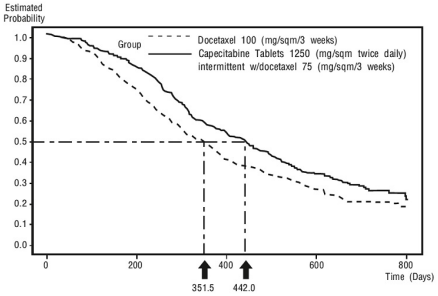


Figure 5 Kaplan-Meier Estimates of Survival in Metastatic Breast Cancer (Study SO14999)



Single Agent

The efficacy of capecitabine tablets as a single agent was evaluated in an open-label single-arm trial (Study SO14697). Eligible patients had 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 (e.g., patients who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents). Resistance was 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 chemotherapy regimen. Patients received capecitabine tablets 1,255 mg/m^2 orally twice daily for first 14-days of a 21-day treatment cycle. The major efficacy outcome measure was tumor response rate in patients with measurable disease, with response defined as a ≥50% decrease in sum of the products of the perpendicular diameters of bidimensionally measurable disease for at least 1 month.

The baseline demographics are shown in Table 16.

Table 16 Baseline Demographics in Metastatic Breast Cancer (Study SO14697)

	Patients With Measurable Disease (N=135)	**All Patients (N=162)**
Age (median, years)	55	56
Karnofsky Performance Status	90	90
No. Disease Sites		
1 to 2, %	32	37
3 to 4, %	46	43
>5, %	22	21
Dominant Site of Disease		
Visceral[1], %	75	68
Soft Tissue, %	22	22
Bone, %	3	10
Prior Chemotherapy		
Paclitaxel, %	100	100
Anthracycline[2], %	90	91
Fluorouracil, %	81	82
Resistance to Paclitaxel, %	76	77
Resistance to an Anthracycline[2], %	41	41
Resistance to both Paclitaxel and an Anthracycline[2], %	32	31

[1]Lung, pleura, liver, peritoneum

[2]Includes 2 patients treated with an anthracenedione

Efficacy for Study SO14697 are shown in Table 17.

Table 17 Efficacy Results in Metastatic Breast Cancer (Study SO14697)

Efficacy Parameter	**Resistance to Both Paclitaxel and an Anthracycline (N=43)**
Response Rate[1] (95% CI)	25.6% (13.5, 41.2)
Complete Response	0%
Partial Response[1]	11%
Duration of Response[1] Median, months[2] (Range)	5.1 (2.1 to 7.7)

[1] Includes 2 patients treated with an anthracenedione

[2] From date of first response

For the subgroup of 43 patients who were doubly resistant, the median time to progression was 3.4 months and the median survival was 8.4 months. The objective response rate in this population was supported by a response rate of 18.5% (1 CR, 24 PRs) in the overall population of 135 patients with measurable disease, who were less resistant to chemotherapy (see Table 15). The median time to progression was 3.0 months and the median survival was 10.1 months.

14.3 Gastric, Esophageal, or Gastroesophageal Junction Cancer

The efficacy of capecitabine tablets for treatment of adults with unresectable or metastatic gastric, esophageal, or gastroesophageal junction cancer as a component of a combination chemotherapy regimen was derived from studies in the published literature. Capecitabine tablets were evaluated in REAL- 2, a randomized non-inferiority, 2x2 factorial trial, where the major efficacy outcome measure was overall survival, and an additional randomized trial conducted by the North Central Cancer Treatment Group, where the major efficacy outcome measure was objective response rate.

The efficacy of capecitabine tablets for the 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 was derived from studies in the published literature. Capecitabine tablets were evaluated in the ToGA trial [NCT01041404], an open-label, multicenter, randomized trial where the primary efficacy measure was overall survival.

14.4 Pancreatic Cancer

The efficacy of capecitabine tablets for the adjuvant treatment of adults with pancreatic adenocarcinoma as a component of a combination chemotherapy regimen was derived from a study in the published literature. Capecitabine tablets were evaluated in ESPAC-4 trial, a two-group, open-label, multicenter, randomized trial, where the major efficacy outcome measure was overall survival.

15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

Capecitabine tablets, USP are supplied as follows:

- 150 mg, Light Peach color, oval shaped film coated tablets debossed with 'A015' on the one side and '150' on the other side; available in bottles of 30 (NDC 67877-458-30), bottles of 60 (NDC 67877-458-60) and in bottles of 120 (NDC 67877-458-12).
- 500 mg, Light Peach color, oval shaped film coated tablets debossed with 'A016' on the one side and '500' on the other side; available in bottles of 30 (NDC 67877-459-30), bottles of 60 (NDC 67877-459-60) and in bottles of 120 (NDC 67877-459-12).

Storage and Handling

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. KEEP TIGHTLY CLOSED.

Capecitabine tablets are a hazardous drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Increased Risk of Bleeding with Concomitant Use of Vitamin K Antagonists

Advise patients on vitamin K antagonists, such as warfarin, that they are at an increased risk of severe bleeding while taking capecitabine tablets. Advise these patients that INR should be monitored more frequently, and dosage modifications of the vitamin K antagonist may be required, while taking and after discontinuation of capecitabine tablets. Advise these patients to immediately contact their healthcare provider if signs or symptoms of bleeding occur *[see Warnings and Precautions (5.1)]*.

Serious Adverse Reactions from Dihydropyrimidine Dehydrogenase (DPD) Deficiency

Inform patients of the potential for serious and life-threatening adverse reactions due to DPD deficiency and discuss with your patient whether they should be tested for genetic variants of *DPYD* that are associated with an increased risk of serious adverse reactions from the use of capecitabine tablets. Advise patients to immediately contact their healthcare provider if symptoms of severe mucositis, diarrhea, neutropenia, and neurotoxicity occur *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.5)]*.

Cardiotoxicity

Advise patients of the risk of cardiotoxicity and to immediately contact their healthcare provider for new onset of chest pain, shortness of breath, dizziness, or lightheadedness *[see Warnings and Precautions (5.3)]*.

Diarrhea

Inform patients experiencing grade 2 diarrhea (an increase of 4 to 6 stools/day or nocturnal stools) or greater or experiencing severe bloody diarrhea with severe abdominal pain and fever to stop taking capecitabine tablets. Advise patients on the use of antidiarrheal treatments (e.g., loperamide) to manage diarrhea *[see Warnings and Precautions (5.4)]*.

Dehydration

Instruct patients experiencing grade 2 or higher dehydration to stop taking capecitabine tablets immediately and to contact their healthcare provider. Advise patients to not restart capecitabine tablets until rehydrated and any precipitating causes have been corrected or controlled *[see Warnings and Precautions (5.5)]*.

Renal Toxicity

Instruct patients experiencing decreased urinary output or other signs and symptoms of renal toxicity to immediately contact their healthcare provider *[see Warnings and Precautions (5.6)]*.

Serious Skin Toxicities

Instruct patients skin rash, blistering, or peeling to immediately contact their healthcare provider

[see Warnings and Precautions (5.7)].

Palmar-Plantar Erythrodysesthesia Syndrome

Instruct patients experiencing grade 2 palmar-plantar erythrodysesthesia syndrome or greater to stop taking capecitabine tablets immediately and to contact their healthcare provider. Inform patients that initiation of symptomatic treatment is recommended and hand-and-foot syndrome can lead to loss of fingerprints which could impact personal identification *[see Warnings and Precautions (5.8)]*.

Myelosuppression

Inform patients who develop a fever of 100.5°F or greater or other evidence of potential infection to immediately contact their healthcare provider *[see Warnings and Precautions (5.9)]*.

Hyperbilirubinemia

Inform patients who develop jaundice or icterus to immediately contact their healthcare provider *[see Warnings and Precautions (5.10)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with capecitabine tablets and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception during treatment with capecitabine tablets and for 3 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise females not to breastfeed during treatment with capecitabine tablets and for 1 week after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males and females of reproductive potential that capecitabine tablets may impair fertility *[see Use in Specific Populations (8.3)]*.

Hypersensitivity and Angioedema

Advise patients that capecitabine tablets may cause severe hypersensitivity reactions and angioedema. Advise patients who have known hypersensitivity to capecitabine or 5-fluorouracil to inform their healthcare provider *[see Contraindications (4)]*. Instruct patients who develop hypersensitivity reactions or mucocutaneous symptoms (e.g., urticaria, rash, erythema, pruritus, or swelling of the face, lips, tongue or throat which make it difficult to swallow or breathe) to stop taking capecitabine tablets and immediately contact their healthcare provider or to go to an emergency room. *[see Adverse Reactions (6)]*.

Nausea and Vomiting

Instruct patients experiencing grade 2 nausea (food intake significantly decreased but able to eat intermittently) or greater to stop taking capecitabine tablets and to immediately contact their healthcare provider for management of nausea *[see Adverse Reactions (6.1)]*.

Instruct patients experiencing grade 2 vomiting (2 to 5 episodes in a 24-hour period) or greater to stop taking capecitabine tablets immediately and to contact their healthcare provider for management of vomiting *[see Adverse Reactions (6.1)]*.

Stomatitis

Inform patients experiencing grade 2 stomatitis (painful erythema, edema or ulcers of the mouth or tongue, but able to eat) or greater to stop taking capecitabine tablets immediately and to contact their healthcare provider *[see Adverse Reactions (6.1)]*.

Important Administration Instructions

Advise patients to swallow capecitabine tablets whole with water within 30 minutes after a meal. Advise patients and caregivers not to chew, crush, or cut capecitabine tablets. Advise patients if they cannot swallow capecitabine tablets whole to inform their healthcare provider *[see Dosage and Administration (2.7), Warnings and Precautions (5.12)]*.

Drug interactions

Instruct patients not to take products containing folic acid or folate analog products (e.g., leucovorin, levoleucovorin) unless directed to do so by their healthcare provider. Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products *[see Drug Interactions (7.1, 7.2, 7.3)]*.

Manufactured by:
Alkem Laboratories Ltd.,
INDIA.

Distributed by:
Ascend Laboratories, LLC
Parsippany, NJ 07054

Revised: February, 2023

PATIENT INFORMATION

Capecitabine (KAP-e-SYE-ta-been) Tablets, USP

What is the most important information I should know about capecitabine tablets?

Capecitabine tablets can cause serious side effects, including:

- **Increased risk of bleeding when taking capecitabine tablets with blood thinner medicines, such as warfarin**. **Taking capecitabine tablets with these medicines can cause changes in how fast your blood clots and can cause bleeding that can lead to death**. This can happen as soon as a few days after you start taking capecitabine tablets, or later during treatment, and possibly within 1 month after you stop taking capecitabine tablets. This can happen in people whose cancer has spread to the liver (liver metastasis) **and** in people whose cancer has not spread to the liver.
  - Before taking capecitabine tablets, tell your healthcare provider if you are taking warfarin or another blood thinner medicine.
  - If you take warfarin or another blood thinner that is like warfarin during treatment with capecitabine tablets, your healthcare provider should do blood tests more often, to check how fast your blood clots during and after you stop treatment with capecitabine tablets. Your healthcare provider may change your dose of the blood thinner medicine if needed.
  - **Tell your healthcare provider right away if you develop any signs or symptoms of bleeding.**

See "What are the possible side effects of capecitabine tablets?" for more information about side effects.

What are capecitabine tablets?

Capecitabine tablets are a prescription medicine used to treat:

- A kind of cancer called colon or rectal (colorectal) cancer. Capecitabine tablets may be used:
  - alone or in combination with other chemotherapy medicines in people with colon cancer that has spread to lymph nodes in the area close to the colon (Stage III colon cancer), to help prevent your cancer from coming back after you have had surgery.
  - adults with rectal cancer, around the time of your surgery, as a part of chemotherapy and radiation (chemoradiation) treatment when your rectal cancer has spread to nearby tissues (locally advanced).
  - alone or in combination with other chemotherapy medicines, when your colorectal cancer cannot be removed by surgery or has spread to other areas of your body (metastatic).
- A kind of cancer called breast cancer. Capecitabine tablets may be used in people with breast cancer that is advanced or has spread to other parts of the body (metastatic):
  - alone if you are not able to receive an anthracycline medicine or taxane-containing chemotherapy.
  - in combination with docetaxel when you have received anthracycline containing chemotherapy and it is no longer working.
- Kinds of cancer called stomach (gastric), esophageal, or gastroesophageal junction (GEJ) cancer. Capecitabine tablets may be used in adults:
  - in combination with other chemotherapy medicines when your cancer of the stomach, esophagus, or GEJ cannot be removed by surgery or has spread to other parts of the body (metastatic).
  - when your cancer of the stomach, esophagus, or GEJ is metastatic adenocarcinoma, **and:**
    - isHER2-positive,**and**
    - you have not received treatment with capecitabine tablets in combination with other treatments for your metastatic cancer.
- A kind of cancer called pancreatic cancer. Capecitabine tablets may be used to treat adults in combination with other chemotherapy medicines, to help prevent your pancreatic cancer from coming back after you have had surgery.

It is not known if capecitabine tablets are safe and effective in children.

Do not take capecitabine tablets if you:

- have had a severe allergic reaction to fluorouracil or capecitabine. See the end of this leaflet for a complete list of ingredients in capecitabine tablets.

Talk to your healthcare provider before taking capecitabine tablets if you are not sure.

Before taking capecitabine tablets, tell your healthcare provider about all your medical conditions, including if you:

See **"What is the most important information I should know about capecitabine tablets?"**

- have had heart problems.
- have kidney or liver problems.
- are pregnant or plan to become pregnant. Capecitabine tablets can harm your unborn baby.

Females who are able to become pregnant:

- Your healthcare provider should do a pregnancy test before you start treatment with capecitabine tablets.
- Use an effective method of birth control (contraception) during treatment and for 6 months after your last dose of capecitabine tablets. Talk to your healthcare provider about birth control choices that may be right for you during treatment with capecitabine tablets.
- Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with capecitabine tablets.

Males who have female partners who are able to become pregnant should use effective birth control during treatment and for 3 months after your last dose of capecitabine tablets.

- are breastfeeding or plan to breastfeed. It is not known if capecitabine passes into your breast milk. Do not breastfeed during treatment with capecitabine tablets and for 1 week after your last dose of capecitabine tablets.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Capecitabine tablets may affect the way other medicines work, and other medicines may affect the way capecitabine tablets works.

How should I take capecitabine tablets?

- Take capecitabine tablets exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much capecitabine tablets to take and when to take it. The number of days that you will take capecitabine tablets during each treatment cycle and the number of days in each treatment cycle depends on the type of cancer you are being treated for.
- Take capecitabine tablets 2 times a day at the same time each day, about 12 hours apart.
- Take capecitabine tablets within 30 minutes after finishing a meal.
- Swallow capecitabine tablets whole with water. **Do not** chew, cut, or crush capecitabine tablets. See "Eye irritation, skin rash and other side effects with exposure to crushed capecitabine tablets" in the section called "**What are the possible side effects of capecitabine tablets?**"
- If you cannot swallow capecitabine tablets whole, tell your healthcare provider.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with capecitabine tablets if you develop side effects.
- **Do not** take products that contain folic acid or folate analog products, for example, leucovorin or levoleucovorin, during treatment with capecitabine tablets, unless your healthcare provider instructs you to take it.
- If you vomit after taking a dose of capecitabine tablets, do not take another dose at that time. Wait and take your next dose of capecitabine tablets at your scheduled time.
- If you miss a dose of capecitabine tablets, just skip the dose and then take your next dose at your scheduled time.
- If you take too much capecitabine tablets, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of capecitabine tablets?

Capecitabine tablets can cause serious side effects including:

- See "**What is the most important information I should know about capecitabine tablets?**"
- **Serious side effects in people with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency.** People with certain changes in a gene called "DPYD" may have a deficiency of the DPD enzyme. Some of these people may not produce enough DPD enzyme, and some of these people may not produce the DPD enzyme at all.
  - People who do not produce any DPD enzyme are at increased risk of sudden side effects that come on early during treatment with capecitabine tablets and can be serious, and sometimes lead to death. **Call your healthcare provider right away if you develop any of the following symptoms and they are severe**, including:

• sores of the mouth, tongue, throat and esophagus (mucositis)		
• diarrhea	• low white blood cell counts	• nervous system problems.

- People with some DPD enzyme may have an increased risk of serious side effects with capecitabine tablets treatment that can sometimes lead to death.

Your healthcare provider should talk with you about DPYD testing to look for DPD deficiency.

- **Heart problems.** Capecitabine tablets can cause heart problems including: heart attack and decreased blood flow to the heart, chest pain, irregular heartbeats, changes in the electrical activity of your heart seen on an electrocardiogram (ECG), problems with your heart muscle, heart failure, and sudden death. You may have an increased risk of heart problems with capecitabine tablets if you have a history of narrowing or blockage of the coronary arteries (coronary artery disease). **Stop taking capecitabine tablets and call your healthcare provider or go to the nearest hospital emergency room right away if you get any new symptoms of a heart problem including:**

◦ chest pain	◦ dizziness
◦ shortness of breath	◦ lightheadedness

- **Diarrhea.** Diarrhea is common with capecitabine tablets and can sometimes be severe. Stop taking capecitabine tablets and call your healthcare provider right away if the number of bowel movements you have in a day increases by 4 or more bowel movements than what is usual for you, or if you have bowel movements at night. Ask your healthcare provider about what medicines you can take to treat your diarrhea. Stop taking capecitabine tablets if you have severe bloody diarrhea with severe abdominal pain and fever and call you healthcare provider right away.
- **Loss of too much body fluid (dehydration) and kidney failure.** Dehydration can happen with capecitabine tablets and may affect how well your kidneys work. If you take capecitabine tablets with certain other medicines that can cause kidney problems, you may have an increased risk of serious kidney failure that can sometimes lead to death. Your risk of kidney failure may also be increased if you have kidney problems before taking capecitabine tablets.

Nausea, and vomiting are common with capecitabine tablets. If you lose your appetite, feel weak, and have nausea, vomiting, or diarrhea, you can quickly become dehydrated.

Stop taking capecitabine tablets and call your healthcare provider right away if you:

- vomit 2 or more times in a day.
- are only able to eat or drink a little now and then, or not at all due to nausea.
- have diarrhea. See "diarrhea" above.

You may need to receive fluids through your vein (intravenous) to treat your dehydration or receive treatment for kidney failure.

- **Severe skin and mouth reactions.**
  - Capecitabine tablets can cause severe skin reactions that may lead to death. Tell your healthcare provider right away if you develop a skin rash, blister and peeling of your skin. Your healthcare provider may tell you to stop taking capecitabine tablets if you have a serious skin reaction. Do not take capecitabine tablets again if this happens.
  - Capecitabine tablets can also cause "hand and foot" syndrome. Hand and foot syndrome is common with capecitabine tablets and can cause you to have numbness and changes in sensation in your hands and feet, or cause redness, pain, swelling of your hands and feet. Stop taking capecitabine tablets and call your healthcare provider right away if you have any of these symptoms and you are not able to do your usual activities.
  - Hand and foot syndrome can lead to a loss of fingerprints which could impact your identification.
  - You may get sores in your mouth or on your tongue when taking capecitabine tablets. Stop taking capecitabine tablets and call your healthcare provider right away if you get painful redness, swelling, or ulcers in your mouth or tongue, or if you are having problems eating.
- **Decreased white blood cells, platelets, and red blood cell counts. Decreased white blood cells, platelets, and red blood cell counts can happen with capecitabine tablets and can sometimes be severe.** Your healthcare provider will do blood tests during treatment with capecitabine tablets to check your blood cell counts.
  If your white blood cell count is very low, you are at increased risk for infection. Call your healthcare provider right away if you develop a fever of 100.5oF or greater or have other signs and symptoms of infection.
- **Increased level of bilirubin in your blood and liver problems.** Increased bilirubin in your blood is common with capecitabine tablets and can also sometimes be severe. Your healthcare provider will check you for these problems during treatment with capecitabine tablets. Tell your healthcare provider right away if you develop yellowing of your skin or the white part of your eyes.
- **Eye irritation, skin rash and other side effects with exposure to crushed capecitabine tablets.** If you come into contact with (you are exposed to) crushed capecitabine tablets, you may develop side effects including:

◦ eye irritation and swelling	◦ feeling like pins and needles in your hands
◦ skin rash	◦ headache
◦ diarrhea	◦ stomach irritation
	◦ nausea and vomiting

Do not chew, cut, or crush capecitabine tablets. See **"How should I take capecitabine tablets**."

If for any reason your tablets must be cut or crushed, this must be done by your pharmacist or healthcare provider.

Your healthcare provider may decide to decrease your dose, or temporarily or permanently stop capecitabine tablets if you have serious side effects with capecitabine tablets.

The most common side effects in people with colon cancer who take capecitabine tablets alone to help prevent it from coming back include: hand and foot syndrome, diarrhea, and nausea.

The most common side effects in people with metastatic colorectal carcinoma who take capecitabine tablets alone include:

• decreased red blood cell count	• nausea
• diarrhea	• tiredness
• hand and foot syndrome	• stomach-area (abdominal) pain
• increased bilirubin level in your blood	

The most common side effects in people with metastatic breast cancer who take capecitabine tablets in combination with docetaxel include:

• diarrhea	• hair loss
• mouth sores or mouth inflammation	• swelling
• hand and foot syndrome	• stomach-area (abdominal) pain
• nausea and vomiting	

The most common side effects in people with metastatic breast cancer who take capecitabine tablets alone include:

• decreased white blood cell and red blood cell count	• nausea and vomiting
• diarrhea	• tiredness
• hand and foot syndrome	• skin inflammation, including rash

Severe allergic reactions can happen with capecitabine tablets. See "**Do not take capecitabine tablets if you**:" **Stop taking capecitabine tablets and call your healthcare provider right away or go to an emergency room if you have any of the following symptoms of a severe allergic reaction to capecitabine tablets:**

• red itchy welts on your skin (hives)	• skin redness	• swelling of your face, lips, tongue or throat
• rash	• itching	• trouble swallowing or breathing

Capecitabine tablets may cause fertility problems in females and males. This may affect the ability to have a child. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of capecitabine tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store capecitabine tablets?

- Store capecitabine tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep capecitabine tablets in a tightly closed container.
- Ask your healthcare provider or pharmacist how to safely throw away any unused capecitabine tablets.

Keep capecitabine tablets and all medicines out of the reach of children.

General information about the safe and effective use of capecitabine tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use capecitabine tablets for a condition for which it was not prescribed. Do not give capecitabine tablets to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about capecitabine tablets that is written for health professionals.

What are the ingredients in capecitabine tablets?

Active ingredient: Capecitabine, USP

Inactive ingredients: anhydrous lactose, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, and purified water. The light peach film coating contains hydroxypropyl methylcellulose, talc, titanium dioxide, iron oxide yellow and iron oxide red.

Manufactured by:
Alkem Laboratories Ltd.,
INDIA.

Distributed by:
Ascend Laboratories, LLC
Parsippany, NJ 07054

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This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: 02/2023

PT3341-03

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

150 mg Tablet Bottle Label
NDC 67877-458-60
60 TABLETS

500 mg Tablet Bottle Label
NDC 67877-459-12
120 TABLETS

CAPECITABINE

capecitabine tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:67877-458
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
CAPECITABINE (UNII: 6804DJ8Z9U) (CAPECITABINE - UNII:6804DJ8Z9U)	CAPECITABINE	150 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX43802MRT)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics			
Color	PINK	**Score**	no score
Shape	OVAL (OVAL)	**Size**	11mm
Flavor		**Imprint Code**	A015
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:67877-458-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/25/2017	
	NDC:67877-458-60	60 in 1 BOTTLE; Type 0: Not a Combination		

2	NDC:67877-458-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	11/25/2017	
3	NDC:67877-458-12	120 in 1 BOTTLE; Type 0: Not a Combination Product	11/25/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207652	11/25/2017	

CAPECITABINE

capecitabine tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:67877-459
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CAPECITABINE (UNII: 6804DJ8Z9U) (CAPECITABINE - UNII:6804DJ8Z9U)	CAPECITABINE	500 mg

Inactive Ingredients

Ingredient Name	Strength
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX43802MRT)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	

Product Characteristics

Color	PINK	**Score**	no score
Shape	OVAL (OVAL)	**Size**	11mm
Flavor		**Imprint Code**	A015
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:67877-459-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	11/25/2017	
2	NDC:67877-459-60	60 in 1 BOTTLE; Type 0: Not a Combination Product	11/25/2017	
3	NDC:67877-459-12	120 in 1 BOTTLE; Type 0: Not a Combination Product	11/25/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA207652	11/25/2017	

Labeler - Ascend Laboratories, LLC (141250469)

Establishment

Name	Address	ID/FEI	Business Operations
Shilpa Medicare Limited		650644136	MANUFACTURE(67877-458, 67877-459)

Establishment

Name	Address	ID/FEI	Business Operations
Alkem Laboratories Limited		677605851	MANUFACTURE(67877-458, 67877-459)