**Drug Monograph**



## A - Drug Name

# capecitabine

**COMMON TRADE NAME(S):** Xeloda®

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## B - Mechanism of Action and Pharmacokinetics

Capecitabine is an antimetabolite, belonging to the fluoropyrimidine carbamate class. A prodrug of 5-fluorouracil (5FU), capecitabine is converted to its two active metabolites, 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP) by carboxyesterase, cytidine deaminase and thymidine phosphorylase (present in the liver and in tumours). The cytotoxic effect of capecitabine is produced by inhibition of thymidylate formation, essential for DNA synthesis, and inhibiting RNA and protein synthesis.

| | | |
|---|---|---|
| Absorption | Bioavailability | Rapid and extensive. $C_{max}$ 1.5 hours. |
| | Effects with food | Rate and extent of absorption reduced by food. |
| | Time to reach steady state | 14 days. |
| Distribution | Widely distributed. | |
| | Cross blood brain barrier? | Not known |
| | PPB | < 60%; primarily albumin (35%) |
| Metabolism | Capecitabine is extensively bioactivated and metabolized in the liver | |

| | | |
|---|---|---|
| | Active metabolites | Yes (FdUMP and FUTP and others) |
| | Inactive metabolites | Yes |
| Elimination | Urine | 95.5%; 3% unchanged |
| | Feces | 2.6% |
| | Half-life | terminal: 45 minutes |

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## C - Indications and Status

**Health Canada Approvals:**

- First-line treatment metastatic colorectal cancer (monotherapy)
- For the adjuvant treatment of patients with stage III (Dukes' stage C) colon cancer (monotherapy)
- In combination with oxaliplatin for the treatment of metastatic colorectal cancer after failure of irinotecan-containing combination chemotherapy
- Advanced or metastatic breast cancer after failure of standard therapy (including a taxane), unless therapy with a taxane is clinically contraindicated (monotherapy)
- In combination with docetaxel for advanced or metastatic breast cancer after failure of anthracycline-containing chemotherapy

**Other Uses:**

- GI cancers (anal, rectal, small bowel, appendiceal, gastric, pancreatic, biliary tract)
- GI neuroendocrine tumours
- Adrenal, renal cell cancer
- Cancer of unknown primary
- Head and neck cancer

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## D - Adverse Effects

**Emetogenic Potential:** Low – No routine prophylaxis; PRN recommended

**Extravasation Potential:** Not applicable

The following table contains adverse effects reported in ≥ 5% of patients with colon cancer in the adjuvant setting receiving capecitabine as monotherapy. Severe adverse events from other studies or post-marketing may also be included.

| ORGAN SITE | SIDE EFFECT* (%) | ONSET** |
|---|---|---|
| Cardiovascular | Arterial thromboembolism (rare) | E |
| | Cardiotoxicity (<5%) (maybe severe) | E |
| | Venous thromboembolism (rare) | E |
| Dermatological | Alopecia (6%) | E |
| | Palmar-plantar erythrodysesthesia syndrome (PPES) (60%) (maybe severe) | E |
| | Rash (6%) (maybe severe) | E |
| Gastrointestinal | Abdominal pain (10%) | E |
| | Anorexia, weight loss (9%) | E |
| | Constipation (6%) | E |
| | Dehydration (4%) | E |
| | Diarrhea (46%) (maybe severe) | D |
| | Dyspepsia (5%) | E |
| | GI obstruction (<5%) | E |
| | GI perforation (rare) | E |
| | Mucositis (22%) | E |
| | Nausea, vomiting (33%) | E |
| General | Fatigue (15%) | E |
| Hematological | Immune thrombocytopenic purpura (rare) | E |
| | Myelosuppression ± infection, bleeding (2%) (maybe severe, including atypical infection) | E |
| Hepatobiliary | ↑ Bilirubin (19%) (grade 3/4) | |
| | Hepatic failure (<1%) | E |
| Hypersensitivity | Hypersensitivity (<1%) | I |
| Nervous System | Dizziness (5%) (including vertigo) | E |

| | | |
|---|---|---|
| | Dysgeusia (6%) | E |
| | Leukoencephalopathy (very rare) | E |
| | Neuropathy (9%) | E |
| Ophthalmic | Conjunctivitis (5%) | D |
| | Eye disorders (cataract, lacrimal duct stenosis, keratitis - rare) | D |
| Renal | Nephrotoxicity (<1%) | D |

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for capecitabine include hand-foot syndrome, diarrhea, nausea, vomiting, mucositis, ↑ bilirubin, fatigue, abdominal pain, anorexia, weight loss, neuropathy and alopecia.

Patients with very low or absent **dihydropyrimidine dehydrogenase (DPD) deficiency** (rate-limiting enzyme of 5-fluorouracil catabolism) are at increased risk of severe or life-threatening toxicity (i.e. neutropenia, GI and neurotoxicity, including fatalities) and should not receive capecitabine.

**Cardiac toxicity** is similar to that reported for other fluorinated pyrimidines and includes myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. Patients with prior coronary artery disease may be at increased risk.

**Dehydration** has been observed and may cause acute renal failure which can be fatal. Patients with preexisting renal dysfunction, concomitant use of nephrotoxic drugs, and risk factors such as anorexia, nausea, vomiting, or diarrhea are at an increased risk.

The median time to onset of **diarrhea** is 34 days. The diarrhea may respond to standard anti-diarrheal therapy (e.g. loperamide). Patients with severe diarrhea should be closely monitored and given fluid and electrolyte replacement for dehydration as indicated.

**Palmar-plantar erythrodysesthesia** (commonly referred to as hand-foot syndrome) is characterized by numbness, dysesthesia or paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering, and severe pain of the hands and/or feet and is more common in patients also receiving docetaxel. Persistent or severe (grade 2 or higher) hand-foot syndrome may lead to loss of fingerprints, which could impact identification. The median time to onset was 79 days. Dose interruption, subsequent dose reduction and topical emollients (e.g. hand creams, udder balm) may ameliorate the manifestations of hand-foot syndrome. Oral pyridoxine may not be effective in ameliorating hand-foot syndrome in patients receiving capecitabine.

**Severe rashes** have been reported (Stevens-Johnson syndrome, Toxic Epidermal Necrolysis). Capecitabine must be permanently discontinued and the patient treated appropriately.

**Hyperbilirubinemia** has been observed in patients with and without hepatic metastases at baseline, though occurring more frequently in patients with hepatic metastases. The median time to onset for grade 3 or 4 hyperbilirubinemia was 64 days. Transaminase and alkaline phosphatase elevations have also been reported

Very rare cases of **leukoencephalopathy** have been reported.

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## E - Dosing

Refer to protocol by which patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with capecitabine. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

***Adults:***

Doses are given orally approximately 12 hours apart, within 30 minutes after the end of a meal.

**Oral:** 1250 mg/m² BID for 14 days

(Total daily dose 2500 mg/$m^2$)

Refer to CAPEDOCE and XELOX regimen monographs for capecitabine dosing in combination with docetaxel or oxaliplatin.

Dose Calculation According to Body Surface Area

Dose level 1250mg/$m^2$ PER DOSE (2500mg/$m^2$/day):

| **1250 mg/$m^2$ PER DOSE** | Number of tablets to be taken at each dose |
|---|---|

| Surface Area ($m^2$) | Dose (mg)* | 150mg | 500mg |
|---|---|---|---|
| ⩽ 1.26 | 1500 | 0 | 3 |
| 1.27 – 1.38 | 1650 | 1 | 3 |
| 1.39 – 1.52 | 1800 | 2 | 3 |
| 1.53 – 1.66 | 2000 | 0 | 4 |
| 1.67 – 1.78 | 2150 | 1 | 4 |
| 1.79 – 1.92 | 2300 | 2 | 4 |
| 1.93 – 2.06 | 2500 | 0 | 5 |
| 2.07 – 2.18 | 2650 | 1 | 5 |
| > 2.19 | 2800 | 2 | 5 |

*given twice daily

Dose level 1000mg/$m^2$ PER DOSE (2000mg/$m^2$/day):

| **1000 mg/$m^2$ PER DOSE** | | Number of tablets to be taken at each dose | |
|---|---|---|---|
| Surface Area ($m^2$) | Dose (mg)* | 150mg | 500mg |
| ⩽ 1.26 | 1150 | 1 | 2 |
| 1.27 – 1.38 | 1300 | 2 | 2 |
| 1.39 – 1.52 | 1450 | 3 | 2 |
| 1.53 – 1.66 | 1600 | 4 | 2 |
| 1.67 – 1.78 | 1750 | 5 | 2 |
| 1.79 – 1.92 | 1800 | 2 | 3 |
| 1.93 – 2.06 | 2000 | 0 | 4 |
| 2.07 – 2.18 | 2150 | 1 | 4 |
| > 2.19 | 2300 | 2 | 4 |

*given twice daily

## ***Dosage with Toxicity:***

Patients with baseline neutrophil counts of <1.5 x $10^9$/L and/or thrombocyte counts of <100 x $10^9$/L should not receive capecitabine therapy

## Dose Modification Guidelines for monotherapy:

Patients should be informed of the need to interrupt treatment immediately if moderate or severe toxicity occurs. Supportive care should be provided, including loperamide for diarrhea.

Doses should not be re-escalated if reduced for toxicity. Missed or omitted doses of capecitabine should not be replaced.

Dose modifications are mandatory for gastrointestinal, dermatological toxicity, neurotoxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

**Non-hematologic Toxicity:**

| Toxicity | Action During a Course of Therapy | Dose Adjustment for Next Cycle (% of starting dose) |
|---|---|---|
| Grade 1 | Maintain dose level | Maintain dose level |
| Grade 2 | | |
| 1st appearance | Hold until resolved to ≤ grade 1 | 100% |
| 2nd appearance | Hold until resolved to ≤ grade 1 | 75% |
| 3rd appearance | Hold until resolved to ≤ grade 1 | 50% |
| 4th appearance | Discontinue treatment permanently | Not applicable |
| Grade 3 | | |
| 1st appearance | Hold until resolved to ≤ grade 1 | 75% |
| 2nd appearance | Hold until resolved to ≤ grade 1 | 50% |
| 3rd appearance, OR any evidence of Stevens-Johnson syndrome or Toxic epidermal necrolysis | Discontinue treatment permanently | Not applicable |
| Grade 4 | | |
| 1st appearance, including SJS or TEN, OR cardiotoxicity OR acute renal failure | Discontinue permanently<br>OR<br>If physician deems it to be in the patient's best interest to continue and no evidence of Stevens-Johnson syndrome or toxic epidermal necrolysis, interrupt until resolved to ≤ grade 1. | Discontinue<br>OR<br>50% |

| | | |
|---|---|---|
| 2nd appearance OR any occurrence of confirmed leukoencephalopathy | Discontinue permanently | Not applicable |

**Hematologic Toxicity:**

Hold capecitabine during a treatment cycle in the presence of grade 3 or 4 hematologic toxicity.

**Dose modifications for toxicity for combination regimens:**

Refer to the CAPEDOCE and XELOX regimen monographs for capecitabine dose modifications in combination use.

For indicated combinations:

- If a treatment delay is indicated for either agent, then administration of both capecitabine and the other chemotherapy drug should be delayed until the requirement for starting both drugs are met.
- During a treatment cycle, if the toxicities are considered by the physician as unrelated to capecitabine, capecitabine may be continued and the dose of the other agent adjusted according to its product monograph.
- If the other agent needs to be discontinued permanently, capecitabine treatment can be resumed when the requirements for restarting capecitabine are met.

***Dosage with Hepatic Impairment:***

| Hepatic impairment | Capecitabine Dose |
|---|---|
| Mild to moderate impairment | No starting dose adjustment necessary |
| Severe | No data, has not been studied |

***Dosage with Renal Impairment:***

Moderate renal impairment results in an increase in severe toxicity.

| Creatinine Clearance (mL/min) | % of Starting Dose |
|---|---|
| 51 - 80 | 100 % with close monitoring |
| 30 - 50 | 75 % (use with caution) |
| <30 | discontinue |

***Dosage in the elderly:***

No dose adjustment for the starting dose is required but patients should be closely monitored. Older patients (≥ 65 years) are more susceptible to the effects of fluoropyrimidine-based therapies with increased grade 3/4 adverse effects, especially when used in combination.

***Children:***

Safety and efficacy not established.

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## F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- Doses are given orally approximately 12 hours apart, within 30 minutes after the end of a meal.
- Swallow tablets whole; do not crush or cut tablets.
- If a capecitabine dose is missed, skip this and give the next dose at the usual time. Missed or omitted doses should not be replaced.
- Store tablets at 15ºC to 30ºC in the original package.

**Antidote for Capecitabine Overdose:**

**Uridine triacetate** is a prodrug of uridine and is a specific antidote for treating capecitabine overdose or severe early onset toxicities. If available, consider administering as soon as possible (i.e. within 96 hours) for suspected overdose. If not available, treatment is symptomatic and supportive.

For usage approval and supply, contact Health Canada's Special Access Program (SAP) (Phone: 613-941-2108. On-call service is available for emergencies). Uridine triacetate (Vistogard®) is supplied by its manufacturer in the United States (Wellstat Therapeutics).

The recommended dosing and administration for **uridine triacetate** in patients ≥18 years is:

- 10 grams (1 packet of coated granules) orally every 6 hours for 20 doses in total, without regards to meals.
- Granules should not be chewed. They should be mixed with 3 to 4 ounces of soft foods such as applesauce, pudding or yogurt.
- The dose should be ingested within 30 minutes of preparation, followed by at least 4 ounces of water.
- Refer to the prescribing information on dose preparation for NG-tube or G-tube use.

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## G - Special Precautions

**Contraindications:**

- Patients who have a known hypersensitivity to capecitabine, its excipients, 5FU or any ingredient in the formulation or component of the container.
- Patients with severe renal impairment (CrCl <30 mL/min).
- Patients with known near or complete absence of DPD (dihydropyrimidine dehydrogenase) activity. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Concomitant use with sorivudine or related analogues (i.e. brivudine), given potential fatal drug interaction.

**Other Warnings/Precautions:**

- Contains lactose and should not be used in patients with hereditary galactose/glucose/lactase disorders.
- Use with caution in patients with risk factors for dehydration, pre-existing renal dysfunction or on nephrotoxic agents.
- Use with caution in patients with a history of cardiovascular disease as well as patients taking anticoagulants such as warfarin.

- Patients with partial DPD deficiency - use with extreme caution. Refer to the DPD Deficiency Guidance for Clinicians for more information.

**Other Drug Properties:**

- Carcinogenicity: Probable
  The long-term carcinogenic potential of capecitabine has not been studied, although 5FU has potential carcinogenic and mutagenic effects.

**Pregnancy and Lactation:**

- Teratogenicity: Yes
  Observed in animal studies.
- Embryotoxicity: Yes
  Observed in animal studies.
  Capecitabine is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose.
- Excretion into breast milk: Probable
  Observed in animal studies.
- Breastfeeding:
  Not recommended.
  Due to the potential for serious adverse reactions in the breastfed infant, breast-feeding is not recommended during treatment and for **2 weeks** after the last dose.
- Fertility effects: Probable

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## H - Interactions

Capecitabine is converted to active 5-FU by the enzyme DPD. The drug likely inhibits CYP2C9, resulting in possible drug interactions with CYP2C9 substrates.

| AGENT | EFFECT | MECHANISM | MANAGEMENT |
|---|---|---|---|
| sorivudine and chemically related analogues (i.e. brivudine) | ↑ capecitabine toxicity; potentially fatal | Inhibition of DPD by sorivudine | Concomitant use is contraindicated; wait at least 4 weeks after sorivudine (or analogues) treatment before starting capecitabine |
| Phenytoin/Fosphenytoin and CYP 2C9 substrates | ↑ phenytoin levels | Capecitabine may inhibit CYP2C9 | Monitor phenytoin levels; avoid concomitant administration |

| | | | |
|---|---|---|---|
| Warfarin | Abnormal INR/PT bleeding; may occur at anytime | Capecitabine may inhibit CYP2C9; ↑ s-warfarin exposure by 57% | Caution; monitor PT and INR and adjust anticoagulant dose accordingly |
| Proton-pump inhibitors | ↓ capecitabine efficacy (secondary analysis of RCT data showed reduced survival with concurrent use of PPIs) | ↓ capecitabine dissolution and/or absorption | Caution and monitor for reduced effectiveness. Consider switching to an antacid |
| Antacids containing aluminum or magnesium hydroxide | small ↑ in plasma concentration of capecitabine | ↑ rate and extent of absorption | Caution (clinical relevance unknown) |
| Leucovorin | ↑ capecitabine toxicity | Potentiates cytotoxicity without increase in efficacy | Caution and monitor |

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## I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

**Recommended Clinical Monitoring**

| Monitor Type | Monitor Frequency |
|---|---|
| CBC | Baseline and at each visit |
| Renal function tests | Baseline and as clinically indicated |
| INR and/or PT | Baseline and as clinically indicated if patient is on anticoagulants |
| Clinical toxicity assessment for diarrhea, dehydration, infection, stomatitis, rash or hand-foot syndrome, cardiac, hepatic and neurotoxicity | At each visit |

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

**Suggested Clinical Monitoring**

| Monitor Type | Monitor Frequency |
|---|---|
| Liver function tests | Baseline and as clinically indicated (if severe organ failure suspected) |

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## J - Supplementary Public Funding

**ODB - General Benefit (ODB Formulary )**

- capecitabine

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## K - References

Chu MP, Hecht JR, Slamon D. Association of proton pump inhibitors and capecitabine efficacy in advanced gastroesophageal cancer: secondary analysis of the TRIO-013/LOGiC randomized clinical trial. JAMA Oncol 2017 Jun 1;3(6):767-73.

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McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 963-71.

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Prescribing Information: Xeloda® (Capecitabine). South San Francisco, CA: Genentech USA, Inc; February 2019.

The Medical Letter: 40(1039) November 6, 1998: 106-7.

Reigner B, Clive S, Cassidy J, et al. Influence of the antacid Maalox on the pharmacokinetics of capecitabine in cancer patients. Cancer Chemother Pharmacol 1999;43(4):309-15.

**April 2023** Updated DPD deficiency information in the Dosing and Special Precautions sections

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## L - Disclaimer

*Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.*

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