

**Drug Monograph**

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**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 <sub>max</sub> 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:

- Colorectal cancer
- Breast cancer

Refer to the product monograph for a full list and details of approved indications.

### 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  $\geq 5\%$  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.

**Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the [hepatitis B virus screening and management](#) guideline.

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/m<sup>2</sup> BID for 14 days

(Total daily dose 2500 mg/m<sup>2</sup>)

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<sup>2</sup> PER DOSE (2500mg/m<sup>2</sup>/day):

<b>1250 mg/m<sup>2</sup> PER DOSE</b>		Number of tablets to be taken at each dose	
Surface Area (m <sup>2</sup> )	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<sup>2</sup> PER DOSE (2000mg/m<sup>2</sup>/day):

<b>1000 mg/m<sup>2</sup> PER DOSE</b>		Number of tablets to be taken at each dose	
Surface Area (m <sup>2</sup> )	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  $<1.5 \times 10^9/L$  and/or thrombocyte counts of  $<100 \times 10^9/L$  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:**

<b>Toxicity</b>	<b>Action During a Course of Therapy</b>	<b>Dose Adjustment for Next Cycle (% of starting dose)</b>
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Hold until resolved to $\leq$ grade 1	100%
2nd appearance	Hold until resolved to $\leq$ grade 1	75%
3rd appearance	Hold until resolved to $\leq$ grade 1	50%
4th appearance	Discontinue treatment permanently	Not applicable
Grade 3		
1st appearance	Hold until resolved to $\leq$ grade 1	75%
2nd appearance	Hold until resolved to $\leq$ grade 1	50%
3rd appearance, OR any evidence of Stevens-Johnson syndrome or Toxic epidermal necrolysis	Discontinue treatment permanently	Not applicable
Grade 4		
1 <sup>st</sup> appearance, including SJS or TEN, OR cardiotoxicity OR acute renal failure	Discontinue permanently OR 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 $\leq$ grade 1.	Discontinue OR 50%
2 <sup>nd</sup> 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	No starting dose adjustment necessary; monitor closely
Severe	No data, has not been studied



**Dosage with Renal Impairment:**

Moderate renal impairment results in an increase in severe toxicity.

<b>Creatinine Clearance (mL/min)</b>	<b>Capecitabine Dose</b>
51 - 80	No adjustment required (with close monitoring)
30 - 50	75 % of recommended dose (use with caution and close monitoring)
<30	Do not use (Contraindicated)

**Dosage in the elderly:**

No dose adjustment for the starting dose is required but patients should be closely monitored. Older patients ( $\geq 65$  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 15°C to 30°C 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).

The recommended dosing and administration for **uridine triacetate** in patients  $\geq 18$  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; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- 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: Documented in animals
- Embryotoxicity: Documented in animals
- Pregnancy:  
Capecitabine is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for **6 months** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for **3 months** after the last dose.
- Excretion into breast milk: Probable  
Breastfeeding is not recommended during treatment and for **2 weeks** after the last dose.
- Fertility effects: Probable  
Documented in animal studies

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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.

Refer to the [hepatitis B virus screening and management](#) guideline for monitoring during and after treatment.

### **Recommended Clinical Monitoring**

Monitor Type	Monitor Frequency
CBC	Baseline and at each visit
Renal function tests	Baseline, at each visit, and as clinically indicated
Liver 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](#)

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## J - Supplementary Public Funding

### **ODB - General Benefit ([ODB Formulary](#))**

- capecitabine

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**K - References**

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**July 2024** Updated Pregnancy/Lactation and Monitoring 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.

*The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare*

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