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## A DRUG NAME: CAPECITABINE

**SYNONYM(S):** 5'-deoxy-5-fluoro-N-cytidine

**COMMON TRADE NAME(S):** Xeloda® (Roche)

## B MECHANISM OF ACTION AND PHARMACOKINETICS

Capecitabine is an antimetabolite, belonging to the fluoropyrimidine carbamate class and causes cell injury via RNA- and DNA-related mechanisms. It is an orally administered precursor of 5-fluorouracil (5FU). Capecitabine is converted to 5FU by carboxyesterase, cytidine deaminase and thymidine phosphorylase (present in the liver and in tumours). Docetaxel appears to upregulate thymidine phosphorylase. The daily oral administration of capecitabine mimics the continuous intravenous infusion of 5-FU.

### Oral Absorption

- 70%; rapid with  $C_{max}$  1.5 hours.
- Pharmacokinetics are largely dose proportional; insignificant food effect.
- Pharmacokinetics altered with advanced age and renal function, but not with gender, race, performance status, liver function and albumin

### 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 metabolite(s)	Yes (FdUMP and FuTP)
Inactive metabolite(s)	Yes

### Excretion

Capecitabine and its metabolites are excreted predominantly in urine (> 70%); about 3% of an administered dose is excreted in urine as unchanged drug. Fecal excretion is minimal (2.6%)	
Urine	Yes
Terminal $t_{1/2}$	45-60 minutes

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**C INDICATIONS AND STATUS**

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

\* Health Canada approved indication

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**D ADVERSE EFFECTS (Monotherapy; predominantly adjuvant - colorectal)**

ORGAN SITE	SIDE EFFECT	ONSET
Cardiovascular	Edema (9%), cardiac failure (rare)	E
	Cerebrovascular accident/TIA (rare)	E
	Hypotension/hypertension (<5%)	E
	EKG changes/arrhythmias (rare)	E
	Ischemia, infarction, sudden death (rare)	E
	Venous thrombosis (<5%)	E
Dermatologic	<u>Hand-and-Foot Syndrome</u> (60%)	E
	Rash (6%), nail disorder (7%)	E
	Alopecia (6%), hirsutism (rare)	E
	Photosensitivity / radiation recall (rare)	E
	Skin discoloration (7%)	D
Gastrointestinal	<u>Diarrhea</u> (46%), dehydration (7%)	D
	Nausea (33%), vomiting (14%)	E
	Obstruction, ileus, hemorrhage, perforation, typhlitis (rare)	E
	Stomatitis (22%)	E
	Constipation (6%)	E
	Anorexia (9%), weight changes	E
	Abdominal Pain (10%), dyspepsia (5%)	E

<b>D ADVERSE EFFECTS (continued) (Monotherapy; predominantly adjuvant - colorectal)</b>			
<b>ORGAN SITE</b>	<b>SIDE EFFECT</b>		<b>ONSET</b>
Hematologic	Anemia (grades 3&4 - 1%)		E
	Thrombocytopenia (grade 3&4 - 1%)		E
	ITP (rare)		
	Neutropenia (grade 3&4 - 2%)		E
Hepatic	Abnormal LFTs (Grades 3 & 4 - 2%); hepatic failure (rare)		E
	Hyperbilirubinemia (grade 3&4 - 20% )		E
Neurological	Paresthesia, loss of hearing (<5%)		E
	Abnormal taste (6%)		E
	Dizziness (5%), vertigo, drowsiness (<5%)		E
	Tremor, ataxia, myoclonic jerks (<5%)		E
	Headache, insomnia (9%)		E
	Depression, confusion, syncope (<5%)		E
Respiratory	Cough, wheezing (< 5%)		E
	Hoarseness, hiccups, rhinitis (<5%)		E
	Dyspnea (6%)		E
Hypersensitivity	< 5%	I	
Metabolic/Renal	Increased triglycerides (< 5%)		D
	Renal impairment, hematuria (rare)		D
	Low magnesium or potassium (< 5%)		E
	Hypothyroidism		D
	Worsening diabetes (< 5%)		E
Ocular effects	Lacrimal duct stenosis , cataract (rare)		D
	Conjunctivitis (5%), blurred vision (rare)		D

D	<b>ADVERSE EFFECTS (continued) (Monotherapy; predominantly adjuvant –colorectal)</b>		
	ORGAN SITE	SIDE EFFECT	ONSET
	Others	Fatigue (15%)	E
		Myalgia/arthralgia (9%)	E
		Infection (<5%), pain (6%)	E
		Fever / chills (4%)	E

Dose-limiting side effects are underlined.

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 events are **gastrointestinal**, **myelosuppression** and **dermatological**.

The median time to onset of **diarrhea**, a dose-limiting adverse effect of capecitabine, 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. Capecitabine should be held and the dose reduced after recovery ([Section E](#)). Older patients ( $\geq 65$  years) may be at higher risk.

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. The median time to onset was 79 days. Dosage interruption/adjustment is required according to severity. In addition to dose interruption and subsequent dose reduction, topical emollients (e.g. hand creams, udder balm) or oral pyridoxine therapy may ameliorate the manifestations of hand-foot syndrome in patients receiving capecitabine.

**Hyperbilirubinemia** associated with capecitabine therapy occurs more frequently in patients with hepatic metastases.

Patients with **dihydropyrimidine dehydrogenase (DPD) deficiency** (rate-limiting enzyme of 5-fluorouracil catabolism) are at risk in resulting in severe toxicity secondary to reduced drug metabolism. While severe deficiency is rare, 3-4% of the population has some degree of DPD deficiency.

**Cardiac toxicity** is similar to that reported for other fluorinated pyrimidines and includes ECG changes, angina, infarction, EKG changes, dysrhythmias and cardiac failure. The risk may be increased in patients with prior coronary artery disease.

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**E DOSING****Adults:**

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

*Monotherapy:*

q3w: 1250 mg/m<sup>2</sup> PO twice daily for 14 days (Total daily dose 2500 mg/m<sup>2</sup>)

*In combination:*

With oxaliplatin: q3w: capecitabine 1000 mg/m<sup>2</sup> PO twice daily for 14 days

With docetaxel: q3w: capecitabine 1250 mg/m<sup>2</sup> PO twice daily for 14 days

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

E

**DOSING (continued)***Dose Modification Guidelines for monotherapy:*

Do not start treatment with capecitabine unless baseline neutrophil counts are  $< 1.5 \times 10^9/L$  and/or platelet counts of  $< 100 \times 10^9/L$ . 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 and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

<i>Toxicity NCIC Grade</i>	<i>Action During a Course of Therapy</i>	<i>Dose Adjustment for Next Cycle (% of starting dose)</i>
<i>Grade 1</i>	Maintain dose level	Maintain dose level
<i>Grade 2</i> 1 <sup>st</sup> appearance 2 <sup>nd</sup> appearance 3 <sup>rd</sup> appearance 4 <sup>th</sup> appearance	Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	100% 75% 50% -
<i>Grade 3</i> 1 <sup>st</sup> appearance 2 <sup>nd</sup> appearance 3 <sup>rd</sup> appearance	Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	75% 50% -
<i>Grade 4</i> 1 <sup>st</sup> appearance	Discontinue permanently Or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	Discontinue Or 50%
2 <sup>nd</sup> appearance	Discontinue permanently	-

E

**DOSING (continued)**

*Dosage in myelosuppression:* Modify according to protocol by which patient is being treated, if no guidelines available, refer to [Appendix 6](#) (Dosage Modification for Myelosuppression). 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 [Docetaxel](#), [Oxaliplatin](#) monographs and [Docetaxel-capecitabine](#), [CAPOX/XELOX](#) regimen monographs for recommended dose modifications in combination use.

For the 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 are met.
- During a treatment cycle, if the toxicities are considered by the physician as unrelated to capecitabine, may continue capecitabine and adjust the dose of the other agent 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 renal impairment:* Moderate renal impairment results in an increase in severe toxicity.

<i>Creatinine Clearance (mL/min)</i>	<i>% of starting dose</i>
51 - 80	100 % with close monitoring
30 - 50	75 % (use with caution)
<30	CONTRAINDICATED

*Dosage with hepatic impairment:* In patients with mild to moderate hepatic impairment exposure is increased, but no dose adjustment is necessary, although caution should be exercised. Use dose modification table above for increases in bilirubin. The use of capecitabine in patients with severe hepatic impairment has not been studied.

*Dosage in the elderly:* No dose adjustment for the starting dose is required, but patients should be closely monitored and dose modification should be performed as described above. Older patients 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 (see [Appendix 3a](#))**

- Oral self-administration; drug available by outpatient prescription
- Clinical studies performed with capecitabine administered 30 minutes after food. Administering capecitabine on an empty stomach may result in slightly higher exposure and thus toxicity.

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## G

**SPECIAL PRECAUTIONS**

Capecitabine is **contraindicated** in patients who have a known hypersensitivity to capecitabine, its excipients, or 5-fluorouracil, in patients with severe renal impairment (CrCl <30 mL/min), and in patients with known DPD (dihydropyrimidine dehydrogenase) deficiency. Contains lactose and should not be used in patients with hereditary galactose/glucose/lactase disorders.

Elderly patients may experience a greater incidence of grade 3 / 4 events (including gastrointestinal) especially when used in combination with docetaxel or oxaliplatin.

Capecitabine is **clastogenic, teratogenic** and **embryo-lethal** in animal models; thus **pregnancy is contraindicated**. In animals, capecitabine metabolites are found in milk; **nursing** should be discontinued while receiving the drug. Adequate contraception should be used by both sexes during and after (recommended for at least 6 months) treatment with capecitabine. The long-term **carcinogenic** potential of capecitabine has not been studied, although 5-fluorouracil has potential carcinogenic and **mutagenic** effects. **Fertility** may be affected.

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H	INTERACTIONS			
	AGENT	EFFECT	MECHANISM	MANAGEMENT
	Phenytoin /Fosphenytoin and CYP 2C9 substrates	Increased phenytoin levels	Capecitabine may inhibit CYP 2C9	Monitor phenytoin levels, avoid concomitant administration
	Leucovorin	Increased effects	Potentiates cytotoxicity without increase in efficacy	Avoid
	Coumadin	Abnormal INR/PT bleeding; may occur at anytime	Capecitabine inhibits CYP 2C9, ↑ s-warfarin exposure by 57%	Monitor PT and INR and adjust anticoagulant dose accordingly
	Antacids containing aluminium or magnesium hydroxide	Small increase in plasma concentration of capecitabine	Increased rate and extent of absorption	Avoid concomitant administration

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I	RECOMMENDED CLINICAL MONITORING	
	<u>Recommended</u> Clinical Monitoring	<u>Suggested</u> Clinical Monitoring
	<ul style="list-style-type: none"> <li>Regular clinical assessment of diarrhea, infection, stomatitis, hand-foot-syndrome. Grade toxicity using the current <a href="#">NCI Common Toxicity Criteria Version</a>.</li> <li>Baseline and regular CBC.</li> <li>Baseline and regular renal function tests</li> <li>Baseline and regular INR if on anticoagulants</li> </ul>	<ul style="list-style-type: none"> <li>Baseline and regular liver function test (if severe organ failure suspected)</li> </ul>

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