

DRUG NAME: Capecitabine**SYNONYM(S):****COMMON TRADE NAME(S):** XELODA®**CLASSIFICATION:** Antimetabolite*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Capecitabine is a prodrug that is selectively tumour-activated to its cytotoxic moiety, fluorouracil, by thymidine phosphorylase. Fluorouracil is further metabolized to two active metabolites, 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP), within normal and tumour cells. FdUMP inhibits DNA synthesis by reducing normal thymidine production, while FUTP inhibits RNA and protein synthesis by competing with uridine triphosphate.¹ The active moiety of capecitabine, fluorouracil, is cell cycle phase-specific (S-phase).

PHARMACOKINETICS:

Interpatient variability	high interpatient variability ²	
Oral Absorption	Rapidly and almost completely absorbed unchanged from GI tract ³ ; food decreases rate and extent of absorption but the clinical significance is unclear. ^{1,4} Capecitabine is recommended to be taken with food because its efficacy and safety are based on studies when it was given within 30 min after a meal. ⁴	
	time to peak plasma concentration	capecitabine: 1.5 h; fluorouracil: 2 h
Distribution	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	capecitabine and metabolites: <60%
Metabolism	Metabolized in the liver to 5'-deoxy-5-fluorocytidine (5'-DFCR) and then to 5'-deoxy-5-fluorouridine (5'-DFUR) in liver and tumour tissues. 5'-DFUR is activated to fluorouracil mainly at tumour site. Fluorouracil is metabolized to the active metabolites FdUMP and FUTP in normal and tumour cells and to the inactive metabolite α -fluoro- β -alanine (FBAL) by dihydropyrimidine dehydrogenase. Mild to moderate hepatic dysfunction has no clinically significant influence on the pharmacokinetics of capecitabine and its metabolites. ⁵	
	active metabolite(s)	fluorouracil, 5'-DFCR, 5'-DFUR, FdUMP, FUTP
	inactive metabolite(s)	FBAL
Excretion	mainly renal excretion	
	urine	84% in the first 24 h and 96% over 7 days as capecitabine and metabolites ³
	feces	no information found
	terminal half life	capecitabine: 0.75 h; fluorouracil: 0.75 h
	clearance	no information found
Sex	no clinically significant difference	
Elderly	no clinically significant difference on 5'-DFUR and fluorouracil pharmacokinetics	
Ethnicity	similar in black and white patients; no information found with other ethnic groups	

Adapted from standard reference¹ unless specified otherwise.

USES:**Primary uses:**

*Breast cancer

*Colorectal cancer

*Health Canada approved indication

No pediatric indications.

Other uses:Pancreatic cancer^{6,7}**SPECIAL PRECAUTIONS:****Contraindications:**

- history of hypersensitivity reaction to capecitabine or fluorouracil¹
- patients with severe renal dysfunction (CrCl < 30 mL/min).⁸

Caution:

- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** DPD is a rate-limiting enzyme in the metabolism of fluorouracil, the active moiety of capecitabine. DPD deficiency is present in about 3% of cancer patients and follows an autosomal recessive inheritance. DPD deficient patients are at a greater risk of severe capecitabine-related toxicities. Capecitabine should be used with caution in this patient population and may require dose reduction.^{9,10} Currently, screening for DPD deficiency is not readily available.⁹

Special populations: Patients over 65 (particularly over 80) may be more sensitive to the adverse effects of fluorouracil, especially severe GI toxicity (e.g., diarrhea, nausea, vomiting).^{1,11,12} Dose reduction may be required.¹³

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and in mammalian in vitro mutation tests. Capecitabine is clastogenic in human lymphocytes in vitro but not in other mammalian in vivo chromosome tests. Note that fluorouracil is mutagenic in Ames test and clastogenic in mammalian in vivo chromosome test.^{1,11}

Fertility: Studies in animals have shown decreased fertility.^{1,11}

Pregnancy: FDA Pregnancy Category D.¹¹ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended because significant amounts of capecitabine metabolites have been found in breast milk in animal studies.¹

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
blood/bone marrow	anemia (72-80%, severe 2-4%)
	lymphopenia (94%, severe 37 [*] -59 [†] %)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	neutropenia (21-26%, severe 4%)
	thrombocytopenia (20-24%, severe 1-4%)
cardiovascular (general)	cardiotoxicity (3%, severe 1%) ¹⁴ ; see paragraph following Side Effects table
	edema (5-9%, severe 1%)
coagulation	idiopathic thrombocytopenic purpura (severe 1%)
constitutional symptoms	fatigue (32-41%, severe 3-8%)
	fever (9-12%, severe 1%)
dermatology/skin	alopecia (6%)
	fingerprint loss ¹⁵⁻¹⁸ ; see paragraph following Side Effects table
	hand-foot skin reaction (53-57%, severe 11-17%); see paragraph following Side Effects table
	nail changes (7%, severe 0%)
	photosensitivity (rare)
	radiation recall reaction (rare)
	rash (24-37%, severe 1%)
	skin discoloration (7%, severe 0%)
gastrointestinal	<i>emetogenic potential</i> : low moderate ¹⁹
	anorexia (20-23%, severe 1-3%)
	constipation (7-15%, severe 1%)
	dehydration (4-7%, severe 2-4%)
	diarrhea (49-57%, severe 15%)
	dyspepsia (8%, severe 0%)
	nausea (38 ⁻ -53 ⁺ %, severe 4%)
	stomatitis (25%, severe 2-7%)
	vomiting (23 ⁻ -37 ⁺ %, severe 4%)
hepatic	alkaline phosphatase elevation (29%) ²⁰
	ALT elevation (15%, severe 3%) ²⁰
	AST elevation (26%) ²⁰
	hyperbilirubinemia (22 ⁺ -49 ⁺ %, severe 19%); see paragraph following Side Effects table
metabolic/laboratory	hypocalcemia (severe 2%) ²¹
neurology	dizziness (5-8%, severe 0%)
	insomnia (8%, severe 0%)
	paresthesia (9-21%, severe 1%)
	sensory disturbance (6%, severe 0%)
ocular/visual	eye irritation/conjunctivitis ²⁰ (11%, severe 3%)
pain	abdominal pain (17-20%, severe 4%)
	headache (9%, severe 1%)
	limb pain (6%, severe 1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	myalgia (9%, severe 0%)
pulmonary	dyspnea (6%, severe 0%)

Adapted from standard reference¹ unless specified otherwise.

Cardiotoxicity occurs in 3% of patients treated with capecitabine and can be fatal.^{14,22} The spectrum of cardiotoxicity is similar to that reported with 5-fluorouracil (5-FU) and includes myocardial infarction, angina, dysrhythmias, cardiac arrest, cardiac failure and ECG changes.²³ Symptoms often occur within 2-3 days after capecitabine is started. The mechanism of capecitabine-related cardiotoxicity is not known.²⁴ Risk factors include a history of cardiotoxicity associated with 5-FU therapy, and a prior history of coronary artery disease.^{23,24} Management includes discontinuation of capecitabine.^{14,22,24}

Hand-foot skin reaction (also known as hand-and-foot syndrome, palmar-plantar erythrodysesthesia, and PPE) refers to a condition where the palms of the hands and soles of the feet become dry, furrowed, red, numb, and tingling, with or without associated swelling. The reaction may interfere with daily activities, especially when blistering, moist desquamation (shedding of scales or small sheets of skin), severe pain, or ulceration occurs.^{12,21} The exact mechanism of the reaction is unknown, although manual labour or vigorous exercise may exacerbate the condition.¹² It usually appears during the early cycles but can also occur in later cycles of capecitabine. Symptoms may manifest at any time within a treatment cycle or in between cycles and usually improve with interruption of capecitabine.^{12,21} When hand-foot skin reaction of \geq grade 2 severity (skin changes with pain but not interfering with function) occurs, capecitabine therapy should be interrupted immediately and resumed at a reduced dose when the toxicity resolves to grade 0-1.²⁵ Limited data are available on the prevention and management of hand-foot skin reaction but the following measures have been suggested:

- avoid tight-fitting shoes or repetitive rubbing pressure to hands and feet, such as that produced by strenuous activities
- apply lanolin-containing creams (eg, Bag Balm®, Udderly Smooth®) liberally and frequently to affected areas¹²
- although vitamin B₆ (pyridoxine) 50-150 mg orally daily was previously proposed for the prevention of paresthesias²⁶⁻²⁸, current evidence suggests that pyridoxine is not effective.^{29,30}

Loss of fingerprints (adermatoglyphia) has been observed in some patients treated with capecitabine. Digits show a smooth red skin surface, with or without distal fissures, and fingerprints cannot readily be observed. Onset of adermatoglyphia is variable, but appears to always be associated with the development of hand-foot syndrome. The incidence of severe adermatoglyphia, however, is not related to the severity of hand-foot syndrome, and may occur with any grade hand-foot syndrome. Duration of adermatoglyphia is also variable. Some patients experience reversal of the effect within weeks of discontinuation of capecitabine, while others exhibit a more persistent effect (e.g., continuing 2 years or more after drug discontinuation). The significance of capecitabine-induced adermatoglyphia is the loss of fingerprint identification as well as the loss of the functional quality of the fingertip in scanning technology.¹⁵⁻¹⁸

Severe **hyperbilirubinemia** has been reported, with twice the prevalence in patients with liver metastases.¹ Concurrent elevations in alkaline phosphatase and/or transaminases may occur with hyperbilirubinemia.^{20,21} If hyperbilirubinemia of \geq grade 2 severity (serum bilirubin > 1.5 times the normal upper limit) occurs, capecitabine therapy should be interrupted immediately until hyperbilirubinemia resolves; dosage reduction may be needed for subsequent capecitabine doses. The effect of severe hepatic dysfunction on capecitabine is unknown.^{1,5,11}

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
docetaxel ²	no pharmacokinetic interactions		
magnesium and aluminum hydroxide-containing antacid (eg, MAALOX®)	no significant influence on capecitabine pharmacokinetics ³¹		magnesium and aluminum hydroxide-containing antacids can be taken with capecitabine if needed ³¹ ; other antacids may need to be taken two hours apart from capecitabine ¹²
paclitaxel ³²	no pharmacokinetic interactions		
phenytoin and fosphenytoin	increased serum phenytoin levels	unknown	monitor serum phenytoin level regularly and monitor patients closely for phenytoin toxicities during concurrent therapy
proton pump inhibitors ^{33,34}	may reduce pharmacological effect of capecitabine	sustained elevation of gastric pH may reduce the dissolution and absorption of capecitabine	clinical significance is unclear ^{31,33-36} no intervention is considered necessary; however, if a cautious approach is preferred, alternative regimens with antacids can be considered ³¹
warfarin ^{37,38}	S-warfarin AUC increased by 57%, clearance reduced by 37%; reports of altered PT, INR and increased bleeding ^{37,39}	probable inhibition of CYP 2C9 by capecitabine ³⁷	monitor INR regularly during therapy (e.g., weekly) and up to 1 month after stopping capecitabine ⁴⁰ ; adjust warfarin dose as needed and increase monitoring as indicated

Adapted from reference¹ unless specified otherwise.

SUPPLY AND STORAGE:

Oral: Hoffmann-La Roche Limited supplies capecitabine as 150 mg and 500 mg film-coated tablets. Tablets contain lactose. Store at room temperature.⁴¹

Additional information: For patients with swallowing difficulties, capecitabine **oral solution** may be created by dissolving the tablets in water (suggest 50 mL water per 500 mg tablet). Stir until tablets completely dissolve (approximately 15 minutes). The bitter taste of the solution may be masked with fruit juice. Grapefruit juice should NOT be used. Solution should be consumed immediately after preparation. Following consumption of the dose, the cup should then be rinsed with water and the resulting contents also consumed to ensure administration of the full dose.⁴²

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:BC Cancer usual dose noted in **bold, italics**

Oral: Cycle Length: 3 weeks^{1,7,25}: 1250 mg/m² (range 313-1250 mg/m²) PO twice a day for 14 consecutive days starting on day 1 (total dose per cycle 35 000 mg/m² [range 8764-35 000 mg/m²]).

For dose level of 1250 mg/m², round dose according to dose calculation table below; for other dose levels, round off to the nearest 150 mg.

Administer within 30 min following the end of a meal.¹

Capecitabine dose calculation according to BSA¹:

dose level 1250 mg/m ² twice a day		number of tablets per dose	
surface area (m ²)	single dose (mg)	150 mg	500 mg
≤1.25	1500	0	3
1.26-1.37	1650	1	3
1.38-1.51	1800	2	3
1.52-1.65	2000	0	4
1.66-1.77	2150	1	4
1.78-1.91	2300	2	4
1.92-2.05	2500	0	5
2.06-2.17	2650	1	5
≥2.18	2800	2	5

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression".

*Dosage in hand-foot skin reaction*²³:

Adverse event		1st event dose*	2nd event dose*	3rd event dose*	4th event dose*
grade	hand-foot skin reaction				
1	Skin changes (e.g., numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	100%	100%	100%	100%
2	Skin changes (e.g., erythema, swelling) with pain affecting activities of daily living	delay then 100%	delay then 75%	delay then 50%	discontinue
3	Severe skin changes (e.g., moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	delay then 75%	discontinue or delay then 50%	discontinue	discontinue

* as a percentage of the original starting dose

BC Cancer usual dose noted in ***bold, italics*****Cycle Length:**

Doses omitted for toxicity should not be replaced. Instead, the patient should resume the originally planned treatment. For example, if treatment is interrupted on day 3 of a 14-day course, the patient would still take the last dose of capecitabine on day 14. Once the dose has been reduced, it should not be increased at later time.¹ For example, if the original starting dose level of 1250 mg/m² dose was reduced to 625 mg/m² during a treatment cycle, then the dose for subsequent cycles should not exceed 625mg/m².

Dosage in renal failure:

- mild renal dysfunction (CrCl 50-80 mL/min): no dose adjustment required^{41,43}
- moderate renal dysfunction (CrCl 30-50 mL/min): reduce starting dose to 75% of recommended dose^{41,43}
- severe renal dysfunction (CrCl <30 mL/min): contraindicated by manufacturer^{41,43}; has been used⁴⁴

Creatinine clearance (mL/min)	Dose
>65	100%
55-65	75%
25-54	50%
<25	discontinue

calculated creatinine clearance = $\frac{N * (140 - \text{Age}) * \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:

- no dose adjustment required for mild to moderate hepatic dysfunction due to liver metastases.^{1,5}
- severe hepatic dysfunction: no information found

Dosage in dialysis:

has been used⁴⁴

Children:

no information found

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