Drug Name | Mechanism of Action & Pharmacokinetics | Indications & Status | Adverse Effects | Dosing | Administration Guidelines | Special Precautions | Interactions | Recommended Clinical Monitoring | References

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 (5-FU). It is converted to 5FU by carboxyesterase, cytidine deaminase and thymidine phosphorylase (present in the liver and in tumours). The daily oral administration of capecitabine mimics the continuous intravenous infusion of 5-FU.

Oral Absorption	• At least 70% • Rapidly absorbed after oral administration, with peak blood levels at 1.5 hrs and peak 5-FU levels in about 2 hours • Pharmacokinetics are largely dose proportional • Administration with food decreases the rate of absorption with minor decreases in the AUC's of 5-DFUR and 5-FU. • Gender, race, performance status, liver function and albumin levels have no effect on pharmacokinetics; pharmacokinetics of metabolites are altered in the presence of advanced age and renal dysfunction
Distribution	Capecitabine or its metabolites are distributed in intestinal mucosa, plasma, liver and other tissues. Cross blood brain barrier? — Not known PPB — < 60% (albumin)
Metabolism	Capecitabine is extensively bioactivated and metabolised 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

* In combination with docetaxel for advanced or metastatic breast cancer after prior anthracyclines

* Advanced or metastatic breast cancer after failure of standard therapy (including a taxane), unless therapy with a taxane is clinically contraindicated

* *Health Canada approved indication*

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D ADVERSE EFFECTS (Monotherapy)

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	Hand-and-Foot Syndrome (60%)	E	
	Rash (6%), Nail disorder (7%)	E	
	Alopecia (6%), hirsutism (rare)	E	
	Photosensitivity / radiation recall (rare)	E	
	Skin discoloration (7%)		D
Gastrointestinal	Diarrhea (57%; severe 15%)		D
	Nausea (53%; severe 4%)	E	
	Vomiting (37%; severe 4%)	E	
	Stomatitis (25%)	E	
	Obstruction, hemorrhage, perforation (rare)		
	Constipation (15%)	E	
	Dehydration (7%)	E	
	Anorexia (23%), weight changes	E	
	Abdominal Pain (20%), dyspepsia (8%)	E	

D **ADVERSE EFFECTS (continued) (Monotherapy)**

ORGAN SITE	SIDE EFFECT	ONSET	
Hematologic	Anemia (grades 3&4 - 4%)	E	
	Thrombocytopenia (grade 3&4 - 2%)	E	
	ITP (rare)		
	Neutropenia (grade 3&4 - 4%)	E	
Hepatic	Abnormal LFTs (Grades 3 & 4 - <5%); hepatic failure (rare)	E	
	Hyperbilirubinemia (grade 3&4 22%)	E	
Neurological	Paresthesia, (21%), loss of hearing (<5%)	E	
	Taste abnormal (6%)	E	
	Dizziness (8%), vertigo, drowsiness (<5%)	E	
	Tremor, ataxia, myoclonic jerks (<5%)	E	
	Headache, insomnia (<10%)	E	
	Depression, confusion, syncope (<5%)	E	
Respiratory	Cough, wheezing (< 5%)	E	
	Hoarseness, hiccups, rhinitis (<5%)	E	
	Dyspnea (6%)		
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 (rare)		D
	Eye irritation (15%), blurred vision (rare)		D

D ADVERSE EFFECTS (continued) (Monotherapy)

ORGAN SITE	SIDE EFFECT	ONSET
Others	Fatigue (41%)	E
	Myalgia/arthralgia (< 10%)	E
	Infection (<5%), pain (6%)	E
	Fever / chills (12%)	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)

In general, adverse events associated with capecitabine were of mild to moderate intensity. The most common events are **gastrointestinal** and **dermatological**.

The median time to onset of **diarrhea**, a dose limiting adverse effect of capecitabine, is 31 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 (≥ 65years) may be more at 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. 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 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:

The recommended dose of capecitabine is 1,250 mg/m^2 administered twice daily for 14 days followed by a 7 day rest period (therefore given as 3 week cycles). Dose is given orally approximately 12 hours apart, within 30 minutes after the end of a meal. Lower doses may be used in combination, refer to the specific regimen for details. For adjuvant therapy, continue for 8 cycles (or 24 weeks); for advanced/metastatic disease continue until progression or unacceptable toxicity.

E DOSING (continued)

Dose Calculation According to Body Surface Area

Dose level 2500mg/m^2/day		Number of tablets to be taken at each dose (morning and evening) Given for 14 days in the absence of ≥ grade 2 toxicity, followed by a one week rest period	
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 Modification Guidelines:

Refer to the **Docetaxel** monograph and **Docetaxel-capecitabine** regimen monograph for recommended dose modifications for the combination. Patient should be carefully monitored for toxicity. Supportive care should be provided, including loperamide for diarrhea. Doses should not be re-escalated if reduced for toxicity. Missed doses of capecitabine should not be replaced.

Recommended Dose Modifications
Mandatory for gastrointestinal, dermatological toxicity and hyperbilirubinemia. Practitioner may elect not to reduce dose for other toxicities unlikely to become serious or life-threatening.

Toxicity NCIC Grade	*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 2nd appearance 3rd appearance 4th 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%
Grade 3 1st appearance 2nd appearance 3rd appearance	 Interrupt until resolved to grade 0-1 Interrupt until resolved to grade 0-1 Discontinue treatment permanently	 75% 50%
Grade 4 1st appearance 2nd 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 permanently	 Discontinue Or 50%

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).

Dosage with renal impairment: mild-moderate renal impairment results in increased exposure to metabolites and 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	CONTRAINDICATED

Dosage with hepatic impairment: In patients with mild to moderate hepatic dysfunction due to liver metastases 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 dysfunction has not been studied.

Dosage in the elderly: Older patients are more susceptible to the effects of fluoropyrimidine-based therapies, and patients ≥ 80 years of age may experience more grade 3 or 4 diarrhea compared to younger patients. No dose adjustment for the starting dose is required but patients should be closely monitored and dose modification should be performed as described above. In combination with docetaxel, patients ≥ 60 years have more toxicity.

Children: Safety and efficacy not established.

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F ADMINISTRATION GUIDELINES (see Appendix 3a)

- Oral self-administration; drug available by retail 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 or 5-fluorouracil, in patients with severe renal impairment (CrCl <30 mL/min), and in patients with known DPD (dihydropyrimidine dehydrogenase) deficiency.

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

Capecitabine is **clastogenic, mutagenic**, **teratogenic** and **embryolethal** 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 before, during and after (for recommended at least 6 months) treatment with capecitabibne. The long-term **carcinogenic** potential of capecitabine has not been studied, although 5-fluorouracil has potential carcinogenic effect. Its effect on **fertility** has also not been established.

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H INTERACTIONS

AGENT	EFFECT	MECHANISM	MANAGEMENT
Phenytoin /Fosphenytoin and CYP 2C9 substrates	Increase phenytoin level	Effects on CYP 2C9	Monitor phenytoin level, if possible avoid concomitant administration
Leucovorin	Increased effects	Potentiates cytotoxicity without increase in efficacy	Avoid
Coumadin anticoagulants	Altered coagulation parameters and or bleeding	Effects on CYP 2C9	Monitor PT and INR
Antacids containing aluminium or magnesium hydroxide	Small increase plasma concentration of capecitabine	Increased rate of absorption	Avoid concomitant administration

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I RECOMMENDED CLINICAL MONITORING

Recommended Clinical Monitoring	**Suggested Clinical Monitoring**
• Regular clinical assessments and grading of diarrhea, stomatitis, hand-foot-syndrome • CBC before next cycle • Baseline renal function test	• Baseline liver function test (if severe organ failure suspected) • Periodic renal function test

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