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-fluororuidine (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	

This document may not be reproduced in any form without the express written permission of BC Cancer Provincial Pharmacy.
Developed: 2001
Revised: 1 June 2023

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 reference[1] unless specified otherwise.

USES:

Primary uses:

*Breast cancer

*Colorectal cancer

Other uses:

Pancreatic cancer[6,7]

*Health Canada approved indication

No pediatric indications.

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to capecitabine or fluorouracil[1]
- complete or near complete absence of dihydropyrimidine dehydrogenase (DPD) activity[8-10]

Caution:

- ***dihydropyrimidine dehydrogenase (DPD) deficiency*** may result in life-threatening or fatal toxicity in patients receiving capecitabine or fluorouracil[9,10]

Special populations: Patients over 65 years (and particularly over 80 years) may be more sensitive to the adverse effects of fluorouracil, especially severe GI toxicity (e.g., diarrhea, nausea, vomiting).[1,13,14] Dose reduction may be required.[15]

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.[1,13]

Fertility: Studies in animals have shown decreased fertility.[1,13]

Pregnancy: FDA Pregnancy Category D.[13] 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.

This document may not be reproduced in any form without the express written permission of BC Cancer Provincial Pharmacy.
Developed: 2001
Revised: 1 June 2023

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†%)
	neutropenia (21-26%, severe 4%)
	thrombocytopenia (20-24%, severe 1-4%)
cardiovascular (general)	cardiotoxicity (3%, severe 1%)[16]; 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.[17-20]; 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	*emetogenic potential:* low moderate[21]
	anorexia (20-23%, severe 1-3%)
	constipation (7-15%, severe 1%)
	dehydration (4-7%, severe 2-4%)
	diarrhea (49-57%, severe 15%); see paragraph following **Side Effects** table
	dyspepsia (8%, severe 0%)
	nausea (38*-53†%, severe 4%)
	stomatitis (25%, severe 2-7%)
	vomiting (23*-37†%, severe 4%)
hepatic	alkaline phosphatase elevation (29%)[22]
	ALT elevation (15%, severe 3%)[22]
	AST elevation (26%)[22]
	hyperbilirubinemia (22†-49*%, severe 19%); see paragraph following **Side Effects** table
metabolic/laboratory	hypocalcemia (severe 2%)[23]
neurology	dizziness (5-8%, severe 0%)
	insomnia (8%, severe 0%)
	paresthesia (9-21%, severe 1%)
	sensory disturbance (6%, severe 0%)

This document may not be reproduced in any form without the express written permission of BC Cancer Provincial Pharmacy.
Developed: 2001
Revised: 1 June 2023

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
ocular/visual	eye irritation/conjunctivitis[22] (11%, severe 3%)
pain	abdominal pain (17-20%, severe 4%)
	headache (9%, severe 1%)
	limb pain (6%, severe 1%)
	myalgia (9%, severe 0%)
pulmonary	dyspnea (6%, severe 0%)

Adapted from standard reference[1] unless specified otherwise.

Cardiotoxicity occurs in 3% of patients treated with capecitabine and can be fatal.[16,24] 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.[25] Symptoms often occur within 2-3 days after capecitabine is started. The mechanism of capecitabine-related cardiotoxicity is not known.[26] Risk factors include a history of cardiotoxicity associated with 5-FU therapy, and a prior history of coronary artery disease.[25,26] Management includes discontinuation of capecitabine.[16,24,26]

Diarrhea is commonly reported and can sometimes be severe. Patients can rapidly become dehydrated if diarrhea is not well managed, so early recognition and management of the symptoms is important. Capecitabine should be immediately withheld for grade 2 or higher diarrhea. Consider early initiation of standard antidiarrheal agents (e.g., loperamide) as indicated. Capecitabine may be restarted if diarrhea resolves or decreases to grade 1 in intensity.[8]

Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency is a rare inherited disorder of pyrimidine metabolism. Capecitabine and fluorouracil are fluoropyrimidines that are metabolized and inactivated by DPD. Reduced DPD activity is associated with the accumulation of active metabolites of these drugs, putting patients at increased risk of early, severe, and life-threatening toxicities with standard doses. Therefore, capecitabine and fluorouracil are contraindicated in patients with complete or near-complete absence of DPD enzyme activity.[9,10] The DPYD gene encodes the DPD enzyme. DPYD genotyping is now available to assess a patient's enzymatic phenotype to guide capecitabine and fluorouracil dosing.[27-29] Note that trifluridine-tipiracil also contains a fluoropyrimidine (trifluridine). However, trifluridine is metabolized by thymidine phosphorylase rather than DPD and as a result, dosing of trifluridine-tipiracil is not affected by DPD deficiency.[30] For further information on capecitabine and fluorouracil dosing, see BC Cancer ***Fluorouracil and Capecitabine Dosing based on DPYD Activity Score*** in Cancer Drug Manual Appendix.

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.[14,23] The exact mechanism of the reaction is unknown, although manual labour or vigorous exercise may exacerbate the condition.[14] 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.[14,23] When hand-foot skin reaction of ≥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.[31] 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 (e.g., Bag Balm®, Udderly Smooth®) liberally and frequently to affected areas[14]
- although vitamin B_6 (pyridoxine) 50-150 mg orally daily was previously proposed for the prevention of paresthesias[32-34], current evidence suggests that pyridoxine is not effective.[35,36]

This document may not be reproduced in any form without the express written permission of BC Cancer Provincial Pharmacy.
Developed: 2001
Revised: 1 June 2023

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.[17-20]

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.[22,23] If hyperbilirubinemia of ≥ 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.[1,5,13]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
allopurinol[37-39]	may reduce conversion of capecitabine to active metabolites; possible decreased efficacy of capecitabine	allopurinol may competitively inhibit orotate phosphoribosyltransferase, the enzyme responsible for formation of FdUMP and FUTP following activation of fluorouracil[38]	clinical significance is unclear[38,40,41]
docetaxel[2]	no pharmacokinetic interactions		
magnesium and aluminum hydroxide-containing antacid (e.g., MAALOX®)	no significant influence on capecitabine pharmacokinetics[42]		magnesium and aluminum hydroxide-containing antacids can be taken with capecitabine if needed[42]; other antacids may need to be taken two hours apart from capecitabine[14]
paclitaxel[43]	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[44,45]	may reduce pharmacological effect of capecitabine	sustained elevation of gastric pH may reduce the dissolution and absorption of capecitabine	clinical significance is unclear[42,44-47] no intervention is considered necessary; however, if a cautious approach is preferred, alternative regimens with antacids can be considered[42]

This document may not be reproduced in any form without the express written permission of BC Cancer Provincial Pharmacy.
Developed: 2001
Revised: 1 June 2023

AGENT	EFFECT	MECHANISM	MANAGEMENT
warfarin[48,49]	S-warfarin AUC increased by 57%, clearance reduced by 37%; reports of altered PT, INR and increased bleeding[48,50]	probable inhibition of CYP 2C9 by capecitabine[48]	monitor INR regularly during therapy (e.g., weekly) and up to 1 month after stopping capecitabine[51]; adjust warfarin dose as needed and increase monitoring as indicated

Adapted from reference[1] 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.[52]

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.[53]

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***

	Cycle Length:	
Oral:	***3 weeks***[1,7,31]:	***1250 mg/m²*** (range 313-1250 mg/m^2) ***PO twice a day for 14 consecutive days*** starting on day 1 (total dose per cycle 35,000 mg/m^2 [range 8764-35,000 mg/m^2]). Take with food. Administer within 30 min following the end of a meal.[1]
Dosage in myelosuppression:		modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression".

This document may not be reproduced in any form without the express written permission of BC Cancer Provincial Pharmacy.
Developed: 2001
Revised: 1 June 2023

Dosage in hand-foot skin reaction[25]:

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

Doses omitted for toxicity should not be replaced. Instead, the patient should resume the originally planned treatment (e.g., 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] (e.g., if the original starting dose level of 1250 mg/m^2 dose was reduced to 625 mg/m^2 during a treatment cycle, then the dose for subsequent cycles should not exceed 625mg/m^2).

Dosage in renal failure:

- mild renal dysfunction (CrCl 50-80 mL/min): no dose adjustment required[52,54]
- moderate renal dysfunction (CrCl 30-50 mL/min): reduce starting dose to 75% of recommended dose[52,54]
- severe renal dysfunction (CrCl <30 mL/min): contraindicated by manufacturer[52,54]; has been used[55]

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

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

Dosage in hepatic failure:

- mild to moderate hepatic dysfunction due to liver metastases: no dose adjustment required[1,5]
- severe hepatic dysfunction: no information found

Dosage in dialysis: has been used[55]

Children: no information found

This document may not be reproduced in any form without the express written permission of BC Cancer Provincial Pharmacy.
Developed: 2001
Revised: 1 June 2023

REFERENCES:

1. Hoffman-La Roche. XELODA® product monograph. Mississauga, Ontario; 5 July 2000
2. Pronk LC, Vasey P, Sparreboom A, et al. A phase I and pharmacokinetic study of the combination of capecitabine and docetaxel in patients with advanced solid tumours. British Journal of Cancer 2000;83:22-29
3. Judson IR, Beale PJ, Trigo JM. A human capecitabine excretion balance and pharmacokinetic study after administration of a single oral dose of 14C-labelled drug. Investigational New Drugs 1999;17:49-56
4. Reigner B, Verwij J, Dirix L. Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. Clinical Cancer Research 1998;4:941-948
5. Twelves C, Glynne-Jones R, Cassidy J, et al. Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. Clinical Cancer Research 1999;5:1696-1702
6. Herrmann R, Borner M, Morant R, et al. Combining gemcitabine (GEM) and capecitabine (CAP) in advanced pancreatic cancer. Results of a phase I trial (abstract). Proceedings of the American Society of Clinical Oncology 2000;19:1038
7. Cartwright T. A phase II trial of xeloda (capecitabine) in advanced or metastatic pancreatic cancer (abstract). Proceedings of the American Society of Clinical Oncology 2000;19:1026
8. Hoffman-La Roche Limited. XELODA® product monograph. Mississauga, Ontario; 2 July 2019
9. Wörmann B, Bokemeyer C, Burmeister T, et al. Dihydropyrimidine Dehydrogenase Testing prior to Treatment with 5-Fluorouracil, Capecitabine, and Tegafur: A Consensus Paper. Oncol Res Treat 2020;43(11):628-636
10. Negarandeh R, Salehifar E, Saghafi F, et al. Evaluation of adverse effects of chemotherapy regimens of 5- fluoropyrimidines derivatives and their association with DPYD polymorphisms in colorectal cancer patients. BMC Cancer 2020;20(560):1-7
11. Shehata N, Pater A, Tang SC. Prolonged severe 5-fluorouracil-associated neurotoxicity in a patient with dihydropyrimidine dehydrogenase deficiency. Cancer Investigation 1999;17:201-205
12. Lu Z, Zhang R, Carpenter JY. Decreased dihydropyrimidine dehydrogenase activity in a population of patients with breast cancer: implication for 5-fluorouracil -based chemotherapy. Clinical Cancer Research 1998;4:325-329
13. Capecitabine. USP DI. Volume 1. Drug information for the health care professional. 20th ed. Englewood, Colorado: Micromedex, Inc.; 2000
14. Mrozek-Orlowski ME, Frye DK, Sanborn HM. Capecitabine: nursing implications of a new oral chemotherapeutic agent. Oncology Nursing Forum 1999;26(4):753-762
15. BC Cancer Agency Breast Tumour Group. BCCA protocol summary for therapy of metastatic breast cancer using capecitabine (BRAVCAP). Vancouver, British Columbia: BC Cancer Agency; 1 June 2000
16. Van Cutsem E, Hoff PM, Blum JL, et al. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. Ann Oncol 2002;13(3):484-5
17. Cohen PR. Capecitabine-associated loss of fingerprints: report of capecitabine induced adermatoglyphia in two women with breast cancer and review of acquired dermatoglyphic absence in oncology patients treated with capecitabine. Cureus 2017;9(1):e969
18. Wong M, Choo S-, Tan E-. Travel warning with capecitabine. Ann Oncol Advance Access 2009;20(7):1281
19. van Doorn L, Veelenturf S, Binkhorst L, et al. Capecitabine and the risk of fingerprint loss. JAMA Oncol 2017;3(1):122-123
20. Al-Ahwal MS. Chemotherapy and fingerprint loss: beyond cosmetic. The Oncologist 2012;17(2):291-293
21. Mackean M, Planting A, Twelves C. Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients wit advanced and/or metastatic cancer. Journal of Clinical Oncology 1998;16:2977-2985
22. Van Cutsem E, Findlay M, Osterwalder B. Capecitabine, an oral fluoropyrimidine carbamate with substantial activity in advanced colorectal cancer: results of a randomized phase II study. Journal of Clinical Oncology 2000;18:1337-1345
23. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. Journal of Clinical Oncology 1999;17:485-493
24. Kuppens IE, Boot H, Beijnen JH, et al. Capecitabine induces severe angina-like chest pain. Ann Intern Med 2004;140(6):494-5
25. Hoffman-La Roche Limited. XELODA® product monograph. Mississauga, Ontario; 31 July . 2002
26. Frickhofen N, Beck FJ, Jung B, et al. Capecitabine can induce acute coronary syndrome similar to 5-fluorouracil. Ann Oncol 2002;13(5):797-801
27. Amstutz U, Henricks LM, Offer SM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing: 2017 Update. Clin Pharmacol Ther 2018;103(2):210-216
28. Clinical Pharmacogenetics Implementation Consortium, (CPIC). CPIC® Guideline for Fluoropyrimidines and DPYD . Available at: https://cpicpgx.org/guidelines/guideline-for-fluoropyrimidines-and-dpyd/. Accessed April 19, 2023
29. BC Cancer Provincial Systemic Therapy Program. Systemic Therapy Update Newsletter: Fluorouracil and Capecitabine Dosing Based on DPYD Genotyping Activity Score. 26(5) ed. Vancouver, British Columbia: BC Cancer; May 2023
30. Schouten JF, Willems J, Sanders, S. J. W. J., et al. Standard-Dose Trifluridine/Tipiracil as Safe Treatment Alternative in Metastatic Colorectal Cancer Patients With DPD Deficiency. Clin Colorectal Cancer 2021;20(4):359–363
31. Gosala N, Villanueva AR. New guidelines for Xeloda toxicity management (letter). Mississauga, Ontario: Hoffman-La Roche Ltd; 28 March 2000
32. Vukelja SJ, Lombardo FA, James WD, et al. Pyridoxine for the palmar-plantar erythrodysesthesia syndrome. Ann Intern Med 1989;111(8):688-689
33. Fabian CJ, Molina R, Slavik M, et al. Pyridoxine therapy for palmar-planter erythrodysesthesia associated with continuous 5-fluorouracil infusion. Invest New Drugs 1990;8(1):57-63

This document may not be reproduced in any form without the express written permission of BC Cancer Provincial Pharmacy.
Developed: 2001
Revised: 1 June 2023

34. Lauman MK, Mortimer J. Effect of Pyridoxine on the Incidence of Palmar Plantar Erythroderma (PPE) in Patients Receiving Capecitabine. Proceedings of the American Society of Clinical Oncology 2001;20(Part 1):392a (abstract 1565)
35. Kang Y, Lee SS, Yoon DH, et al. Pyridoxine is not effective to prevent hand-foot syndrome associated with capecitabine therapy: results of a randomized, double-blind, placebo-controlled study. J Clinl Oncol 2010;28(24):3824-3829
36. von Gruenigen V, Frasure H, Fusco N, et al. A double-blind, randomized trial of pyridoxine versus placebo for the prevention of pegylated liposomal doxorubicin-related hand-foot syndrome in gynecologic oncology patients. Cancer 2010;116(20):4735-4743
37. IBM Micromedex® Drug Interaction Checking (electronic version). Allopurinol and Capecitabine. IBM Watson Health, Available at: http://www.micromedex.com. Accessed 8 April, 2019
38. Lexicomp Online®: Interactions (database on the Internet). Capecitabine/Allopurinol. Wolters Kluwer Clinical Drug Information Inc., Available at: https://online.lexi.com/lco/action/home. Accessed 7Apr, 2021
39. Genentech USA Inc. XELODA® full prescribing information. South San Francisco, CA, USA; February 2019
40. Jansman FGA, Jansen AJA, Coenen JLL, et al. Assessing the clinical significance of drug interactions with fluorouracil in patients with colorectal cancer. Am J Health-Syst Pharm 2005;62(17):1788-1793
41. Fox RM, Woods RL, Tattersall MHN, et al. Allopurinol modulation of high-dose fluorouracil toxicity. Cancer Treat Rev 1979;6(Supplement):143-147
42. Reigner B, Clive S, Cassidy J, et al. Influence of the antacid MAALOX® on the pharmacokinetics of capecitabine in cancer patients. Cancer Chemotherapy and Pharmacology 1999;43(4):309-315
43. Villalona-Calero MA, Weiss GR, Burris HA, et al. Phase I and pharmacokinetic study of the oral fluoropyrimidine capecitabine in combination with paclitaxel in patients with advanced solid malignancies. Journal of Clinical Oncology 1999;17:1915-1925
44. Chu MP, Hecht JR, Slamon D, et al. Association of Proton Pump Inhibitors and Capecitabine Efficacy in Advanced Gastroesophageal Cancer: Secondary Analysis of the TRIO-013/LOGiC Randomized Clinical Trial. JAMA Oncol 2016:2016 Oct 13. doi: 10.1001/jamaoncol.2016.3358. [Epub ahead of print]
45. Sun J, Ilich AI, Kim CA, et al. Concomitant Administration of Proton Pump Inhibitors and Capecitabine is Associated With Increased Recurrence Risk in Early Stage Colorectal Cancer Patients. Clinical Colorectal Cancer 2016;15(3):257-263
46. European Medicines Agency. Assessment Report - Capecitabine Accord. London, United Kingdom; 16 February . 2012
47. Reigner B, Verweij J, Dirix L, et al. Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. Clin Cancer Res 1998;4(4):941-948
48. Hoffman-La Roche Limited. XELODA® product monograph. Mississauga, Ontario; 11 December 2014
49. Camidge R, Reigner B, Cassidy J, et al. Significant effect of capecitabine on the pharmacokinetics and pharmacodynamics of warfarin in patients with cancer. J Clin Oncol 2005;23(21):4719-4725
50. Genentech USA Inc. XELODA® full prescribing information. South San Francisco, CA, USA; March 2015
51. Kolesar JM, Johnson CL, Freeberg BL. Warfarin-5-FU interaction: a consecutive case series. Pharmacotherapy 1999;19(12):1445-1449
52. Hoffman-La Roche Limited. XELODA® product monograph. Mississauga, Ontario; 15 February 2011
53. Lam MSH. Extemporaneous compounding of oral liquid dosage formulations and alternative drug delivery methods for anticancer drugs. Pharmacotherapy 2011;31(2):164-192
54. Poole C, Gardiner J, Twelves C, et al. Effect of renal impairment on the pharmacokinetics and tolerability of capecitabine (XELODA®) in cancer patients. Cancer Chemother Pharmacol 2002;49:225-234
55. Jhaveri KD, Flombaum C, Shah M, et al. A retrospective observational study on the use of capecitabine in patients with severe renal impairment (GFR

This document may not be reproduced in any form without the express written permission of BC Cancer Provincial Pharmacy.
Developed: 2001
Revised: 1 June 2023