DRUG NAME: Fluorouracil

SYNONYM(S): 5-FU, 5-Fluorouracil, NSC-19893

COMMON TRADE NAME: ADRUCIL®, EFUDEX® CREAM

CLASSIFICATION: antimetabolite

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Fluorouracil is an analog of the pyrimidine uracil and thus acts as a pyrimidine antagonist.[1] There are three possible mechanisms of action.[2] First, the fluorouracil metabolite fluorodeoxyuridine monophosphate (FdUMP) competes with uracil to bind with thymidylate synthetase (TS) and the folate cofactor.[3] This results in decreased thymidine production and therefore decreased DNA synthesis and repair, and ultimately decreased cell proliferation. Leucovorin (formyltetrahydrofolate, formyl-FH_4) enhances fluorouracil by stabilizing the binding of FdUMP to TS. Second, the fluorouracil metabolite fluorodeoxyuridine triphosphate (FdUTP) is incorporated into DNA thus interfering with DNA replication.[2] Finally, the fluorouracil metabolite fluorouridine-5-triphosphate (FUTP) is incorporated into RNA in place of uridine triphosphate (UTP), producing a fraudulent RNA and interfering with RNA processing and protein synthesis.[4] Fluorouracil is cell-cycle specific (S-phase).[3]

PHARMACOKINETICS:

Interpatient variability	variations in dihydropyrimidine dehydrogenase (DPD) activity result in differences in toxicity[5]	
Oral Absorption	erratic; 28-100%	
Distribution	approximately 22% of total body water; penetrates extracellular fluid and third space fluids (e.g., malignant effusions and ascitic fluid)	
	cross blood brain barrier?	yes
	volume of distribution[6]	8-11 L/m^2
	plasma protein binding[7]	10%
Metabolism	activated in target cells; 80% degraded in liver by DPD[6]	
	active metabolite(s)	FdUMP, FUTP, and FdUTP
	inactive metabolite(s)	dihydrofluorouracil
Excretion	60-80% excreted as respiratory CO_2; 2-3% by biliary system	
	urine	<10% as intact drug[6]
	terminal half life	IV bolus: 8-14 min
	clearance	IV bolus: 350-850 mL/min/m^2; dependent on dose, schedule, and route of administration; nonlinear pharmacokinetics due to saturable degradation[6]; interference with fluorouracil degradation markedly prolongs its half-life[6] continuous infusion: clearance increases
Ethnicity	DPD deficiency: Caucasian (3-5%); African-American 0.1%[8]	

Adapted from standard references[9,10] unless specified otherwise.

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USES:

Primary uses:
*Actinic keratoses (topical)
*Bladder cancer
*Breast cancer
*Colorectal cancer
*Gastric cancer
*Head and neck cancer
*Ovarian cancer
*Pancreatic cancer
*Prostate cancer
*Skin cancer, basal cell (topical)

Other uses:
Cervical cancer[4]
Esophageal cancer[4]
Ocular cancer (topical)[11]
Renal cell cancer[4]
Skin cancer, Bowen's disease (topical)[12]
Skin cancer, squamous cell (topical)[12]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to fluorouracil[10]
- relatively contraindicated in patients who have a known hypersensitivity to capecitabine[13]
- complete or near complete absence of dihydropyrimidine dehydrogenase (DPD) activity[14-17]

Caution:
- ***dihydropyrimidine dehydrogenase (DPD) deficiency*** may result in life-threatening or fatal toxicity in patients receiving fluorouracil or capecitabine[16,17]
- ***nonlinear pharmacokinetics*** result in unpredictable plasma concentrations and toxicity at high doses[6]
- patients who are receiving ***radiation*** or who have received high-dose pelvic radiation and patients previously treated with alkylating agents may experience more bone marrow suppression[10]

Special populations:
- ***elderly*** patients are at increased risk for developing toxicities, likely due to decreased bone marrow reserve[6]
- ***female*** patients are at increased risk for developing toxicities[6,18,19]

Carcinogenicity: not yet studied[3]

Mutagenicity: Fluorouracil has been shown to be mutagenic in some bacterial strains. It is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[3]

Fertility: The effects of fluorouracil on fertility have not been established.[3]

Pregnancy[10]***:*** FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if 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 due to the potential secretion into breast milk.[9]

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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.[20] When placebo-controlled trials are available, adverse events are included if the incidence is greater than or equal to 5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	anaphylaxis (rare)[3]
	generalized allergic reactions (rare)[3]
blood/bone marrow/ febrile neutropenia	***myelosuppression****: onset: 7-10 days; nadir: 14 days; recovery: 30 days
cardiovascular (arrhythmia)	arrhythmias
	cardiotoxicity* (≤8%)[21]; see paragraph following **Side Effects** table
	chest pain (<1%); ranging from mild angina to crushing pain
	CHF (rare)[3]
	hypotension (<1%)
constitutional symptoms	somnolence (<1%)
dermatology/skin	*extravasation hazard:* irritant[9,10,22,23]
	For side effects following ***topical application to the skin****,* see paragraph following **Side Effects** table
	alopecia (>10%)
	dermatitis* (>10%)
	dry skin and fissuring (1-10%)
	nail changes (<1%); banding or loss of nails
	palmar-plantar erythrodysesthesia (PPE)* (<1%); see paragraph following **Side Effects** table
	photosensitivity (<1%)
	vein hyperpigmentation (<1%); proximal to injection sites
gastrointestinal	*emetogenic potential:* minimal (rare)[24]
	anorexia (>10%)
	diarrhea* (>10%)
	esophagitis (>10%)
	heart burn (>10%)
	nausea (<10%)
	stomatitis* (>10%)
	epithelial ulceration (1-10%)
	vomiting (<10%)
hemorrhage	GI bleeding

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
hepatic	biliary sclerosis[6]
	hepatic toxicity (<1%)
neurology	acute cerebellar ataxia (<1%); increased with high doses or intensive regimens; see paragraph following **Side Effects** table
	neurotoxicities* (<1%)
ocular/visual	excessive lacrimation
	ocular toxicities*; see paragraphs following **Side Effects** table for *ocular toxicity related to systemic and ocular (topical) administration*
pain	headache (<1%)
pulmonary	dyspnea (<1%)

Adapted from standard references[9,10] unless specified otherwise.
*__Severity varies with route of administration__, refer to the paragraph "Dosing schedule and toxicity".

Dosing schedule and toxicity: The spectrum of toxicity associated with fluorouracil treatment varies with dose, schedule, route of administration, and whether the fluorouracil is being used with a biochemical modulator.[6] The most commonly seen toxicities when standard doses are administered in the following schedules and routes are:
- monthly bolus administration[25]: myelosuppression can be dose-limiting
- daily bolus administration for 5 days[25]: diarrhea can be dose-limiting; myelosuppression, stomatitis, ocular, and dermatitis[6]
- continuous infusion given over 24 hours to several weeks[25]: diarrhea, and stomatitis can be dose-limiting; myelosuppression, dermatitis, PPE, neurologic, ocular, and cardiotoxicity[10]
- weekly bolus administration[25]: diarrhea can be dose-limiting; myelosuppression, stomatitis,[6] and ocular[26]
- topical daily[6]: local inflammation

In the event of a ***5FU overdose***, appropriate and timely measures to anticipate and implement supportive management of patients at risk for severe 5FU toxicity should be implemented. For further information on management of 5FU overdose, see BC Cancer Management Guideline: ***Management of 5-fluorouracil (5FU) infusion overdose***.

Oral cryotherapy with bolus doses of fluorouracil: It is recommended that patients receiving bolus fluorouracil undergo 30 minutes of oral cryotherapy to decrease the incidence and severity of fluorouracil-induced stomatitis.[27] The incidence can be reduced by 50%.[28] Starting 5 minutes before the injection, the patient is asked to place ice chips into their mouth and swish for 30 minutes, replenishing the ice as it melts. This may cause numbness or headaches which subside quickly. This cooling of the oral cavity leads to vasoconstriction resulting in a lower concentration of fluorouracil reaching the oral mucosa.[27] Oral cryotherapy is not used for infusional fluorouracil as this would be very inconvenient. It is also not used for bolus fluorouracil administered in combination with oxaliplatin. This is due to the concern with oxaliplatin and cold related laryngo-dysesthesias.[20]

Acute cerebellar syndrome can rarely occur and is characterized by an acute onset of ataxia, dysmetria, dysarthria, and nystagmus that develops weeks to months after beginning treatment. These symptoms usually resolve after discontinuation of fluorouracil. Cerebellar syndrome may be partly explained because fluorouracil crosses the blood-brain barrier, and the highest concentrations are found in the cerebellum. Other rarer neurologic side effects include encephalopathy, optic neuropathy, eye movement abnormalities, focal dystonia, cerebrovascular disorders, parkinsonian syndrome, peripheral neuropathy, and seizures.[29]

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Cardiotoxicity[21]: Fluorouracil has the second highest incidence of chemotherapy induced cardiotoxicity, after the anthracyclines.[10] The incidence of fluorouracil induced cardiotoxicity can be as high as 8%.[21] Within this group types of cardiotoxicity include[30]:

- electrocardiographic changes (69%),
- angina (48%),
- myocardial infarction (23%),
- acute pulmonary edema (17%),
- arrhythmias (16%),
- elevated cardiac enzymes (14%), and
- cardiac arrest and pericarditis (2%).

Coronary vasospasm is thought to be the underlying mechanism of this toxicity.[21,31] Although most patients who experience fluorouracil-induced cardiotoxicity have no previous cardiac problems, history of preexisting coronary artery disease is a risk factor. Other risk factors include route of administration (refer to the Dosing schedule and toxicity paragraph following the Side Effect table) and the use of concurrent radiation or anthracyclines.[21] Most cases of fluorouracil-induced cardiotoxicities resolve after termination of fluorouracil infusion and/or administration of nitrates or calcium channel blockers.[31] Rechallenging these patients remains controversial. If rechallenged, these patients needs careful observation during drug infusion and may benefit from treatment with calcium channel blockers or nitrates.[31]

Dihydropyrimidine dehydrogenase (DPD) enzyme deficiency is a rare inherited disorder of pyrimidine metabolism. Fluorouracil and capecitabine 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, fluorouracil and capecitabine are contraindicated in patients with complete or near-complete absence of DPD activity.[16,17] The DPYD gene encodes the DPD enzyme. DPYD genotyping is now available to assess a patient's enzymatic phenotype to guide fluorouracil and capecitabine dosing.[32-34] 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.[35] For further information on fluorouracil and capecitabine dosing, see BC Cancer ***Fluorouracil and Capecitabine Dosing based on DPYD Activity Score*** in Cancer Drug Manual Appendix.

Following systemic administration, fluorouracil-induced ***ocular toxicities*** result primarily from ocular surface problems, such as excessive lacrimation, blurred vision, photophobia, and eye irritation.[25] Excessive lacrimation is the most frequent ocular symptom and can be quite dramatic; it may occur any time during treatment and possibly accompanied with pruritus and burning.[6] Fluorouracil has been found in tear fluid and can cause acute and chronic conjunctivitis leading to tear duct fibrosis. Ocular toxicities can also include epiphora, blepharitis, conjunctivitis, tear duct stenosis, and sclerosing canaliculitis. Applying ice packs to the eyes before, during, and for 30 minutes after fluorouracil injection may decrease ocular toxicity.[25]

Following ***ocular (topical) administration*** of fluorouracil eye drops, commonly reported local side effects may include: pain, tearing, photophobia, and redness. Eyelid edema, conjunctival congestion, and keratopathy have also been reported. Local ocular side effects tend to be mild, reversible, and transient. To minimize contact with healthy skin, an inert topical ointment (such as petrolatum) may be applied to the eyelid and skin around the eye to act as a physical barrier against the active drug. Ocular toxicities are reported to resolve within 4 weeks of treatment end with local application of lubricant eye drops (e.g., artificial tears). Topical corticosteroids may be used with lubricant drops to reduce symptoms.[11,36-38]

Palmar-plantar erythrodysesthesia (PPE), also called hand-foot skin reaction, may occur in association with the continuous infusion of fluorouracil.[9] PPE may gradually disappear over 5-7 days after discontinuance of fluorouracil therapy.[3] Although vitamin B_6 (pyridoxine) 50-150 mg orally daily was previously proposed for the prevention of paresthesias[39-41], current evidence suggests that pyridoxine is not effective.[42,43]

Topical application to the skin leads to the following sequence of effects: erythema, usually followed by vesiculation, erosion, ulceration, necrosis, and epithelization.[44] The lower frequency and intensity of activity in adjacent normal skin indicates a selective cytotoxic property. The most frequent local reactions are pain, pruritus, hyperpigmentation, and burning at the application site. Other local reactions include dermatitis, scarring, soreness,

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and tenderness. Insomnia, stomatitis, suppuration, scaling, swelling, irritability, medicinal taste, photosensitivity, and lacrimation have also been reported.[45]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
allopurinol[46,47]	may reduce conversion of fluorouracil to metabolites (possible loss of fluorouracil efficacy)[46]; however, allopurinol has been used clinically to modulate toxicity of fluorouracil without loss of activity[47-49]	allopurinol may competitively inhibit orotate phosphoribosyl-transferase, the enzyme responsible for formation of FdUMP and FUTP following activation of fluorouracil[50]	clinical significance is unclear[14,47,48,51]
cimetidine[52]	delayed, moderate, possible; fluorouracil efficacy and toxicity may be increased	unknown	monitor for fluorouracil toxicity; discontinue cimetidine if necessary
fosphenytoin[52]	delayed, moderate, possible; fosphenytoin efficacy and toxicity may be increased	inhibition of hydantoin metabolism (CYP2C9) by fluorouracil suspected	monitor fosphenytoin plasma levels; observe clinical response when starting or stopping fluorouracil
gemcitabine[53]	fluorouracil efficacy and toxicity may be increased	unknown	some protocols are designed to take advantage of this effect; monitor toxicity closely
leucovorin[25]	increased cytotoxic and toxic effects of fluorouracil	leucovorin stabilizes the bond to thymidylate synthetase	some protocols are designed to take advantage of this effect; monitor toxicity closely
metronidazole[54]	fluorouracil efficacy and toxicity may be increased	metronidazole may decrease the metabolism of fluorouracil	monitor for fluorouracil toxicity
oxaliplatin[55]	no influence on fluorouracil pharmacokinetics		
phenytoin[52]	delayed, moderate, possible; phenytoin efficacy and toxicity may be increased	inhibition of hydantoin metabolism (CYP2C9) by fluorouracil suspected	monitor phenytoin plasma levels; observe clinical response when starting or stopping fluorouracil
thiazides[52] (e.g., chlorthalidone, hydrochlorothiazide)	delayed, moderate, possible; thiazides may prolong fluorouracil-induced leukopenia	unknown	consider alternative antihypertensive therapy
warfarin[56-59]	elevation of anticoagulation parameters (e.g., PTT, INR) and reports of increased bleeding; effect may be delayed[58]	probable inhibition of CYP 2C9 by fluorouracil[60]	monitor INR regularly during therapy (e.g., weekly)[56]; adjust warfarin dose as needed and increase monitoring if indicated

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SUPPLY AND STORAGE:

Topical:
Valeant Canada Limited supplies fluorouracil in a 5% cream. Other ingredients include: white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, and parabens. Store at room temperature. Protect from light.[15]

Hill Dermaceuticals supplies fluorouracil in a 4% (w/w) cream. Other ingredients include: cetyl and stearyl alcohol, butylated hydroxytoluene, parabens, and peanut oil. Store at room temperature.[61]

Injection:
Sandoz Canada Inc. supplies fluorouracil as a preservative free solution in 500 mg single-use and 5000 mg pharmacy bulk vials in a concentration of 50 mg/mL. Store at room temperature. Protect from light.[62]

Accord Healthcare Inc. supplies fluorouracil as a preservative free solution in 5000 mg pharmacy bulk vials in a concentration of 50 mg/mL. Store at room temperature. Protect from light.[14]

Biolyse Pharma Corp supplies fluorouracil as a preservative free solution in 500 mg single-use and 5000 mg pharmacy bulk vials in a concentration of 50 mg/mL. Store at room temperature. Protect from light.[63]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- slight discolouration does not affect potency or safety[64]
- darker yellow discolouration indicates greater decomposition so dark yellow solutions may need to be discarded[64]
- crystals that have formed in the solution can be redissolved by warming and shaking[64]

Fluorouracil Eye Drops[65,66]
- fluorouracil eye drops 10 mg/mL (1%) can be prepared with normal saline (NS)
- final product is stable for 7 days if stored at room temperature or refrigerated
- to achieve a 10 mg/mL (1%) eye drop solution:
  - withdraw 2 mL (100 mg) from 50 mg/mL vial of fluorouracil
  - transfer the 2 mL (100 mg) to a sterile 15 mL eye dropper bottle
  - add 8 mL NS to the eye dropper bottle to give a concentration of 10 mg/mL (1%)

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
**Direct intravenous*[67,68]	***over 2-4 minutes***
**Intermittent infusion*[10]	***can be used*** (e.g., dilute in 50 mL and infuse for up to 15 minutes)
****Continuous infusion***	***over 24 hours or greater;*** may be given ***via an ambulatory infusion device***

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BC Cancer administration guideline noted in ***bold***, ***italics***

Intraperitoneal[69]	***15 mg/kg and 50 mEq sodium bicarbonate to 1000 mL 1.5% dextrose dialysis solution; dwell for 23 hours then drain for one hour***
Intrapleural	no information found
Intrathecal[1]	contraindicated due to neurotoxicity
Intra-arterial[1]	hepatic artery
Intravesical[3]	portal vein infusion
Ocular (topical)[11,36,37,66]	***instill eye drops in the affected eye*** as per protocol

*Doses prescribed for continuous infusion can be FATAL when given as direct intravenous or intermittent infusion.

TOPICAL ADMINISTRATION:

The cream is applied twice daily, preferably with a nonmetal applicator or glove. If the cream is applied with fingertips, the hands should be washed immediately afterwards. Apply with care near the eyes, mouth and nose. An occlusive dressing is not essential, and may increase the incidence of inflammatory reactions in adjacent normal skin. Therapy is usually continued until the inflammatory reaction reaches the erosion, necrosis, and ulceration stage (2-4 weeks), after which healing occurs over 4-8 weeks. While the patient is undergoing topical 5-FU therapy, consideration can be given to curettage, wound excision and removal of pathological tissue. Patients should avoid prolonged exposure to ultraviolet light while under treatment as the intensity of the reaction may be increased.[45]

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:	
Intravenous:	***1 week***[70,71]***:***	***1000 mg/m² IV over 24 hours for 2 consecutive days*** starting on day 1 (total dose per cycle 2000 mg/m²) (maximum dose is 5000 mg/48 h)
	2 weeks[72-76]***:***	***400 mg/m² IV for one dose on day 1 immediately followed by 2400-3000 mg/m² IV over 46 hours*** (total dose per cycle 2800-3400 mg/m²)
	3 weeks[77-84]***:***	***500-600 mg/m² IV for one dose on day 1*** (total dose per cycle 500-600 mg/m²)
	3 weeks[85]***:***	***1000 mg/m²IV over 24 hours for 3 consecutive days*** starting on day 1 (total dose per cycle 3000 mg/m²)
	4 weeks[86,87]***:***	***425 mg/m² IV once daily for 5 consecutive days*** starting on day 1 (total dose per cycle 2125 mg/m²)

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

	4 weeks[88,89]***:***	***when given as a dose-dense regimen with filgrastim (G-CSF) support:*** ***500 mg/m² IV for one dose on days 1 and 8*** (total dose per cycle 1000 mg/m²)
	4 weeks[90-92]***:***	***500-600 mg/m² IV for one dose on days 1 and 8*** (total dose per cycle 1000-1200 mg/m²)
	4 weeks[93-96]***:***	***when given as a dose-dense regimen with filgrastim (G-CSF) support:*** ***500 mg/m² IV for one dose on days 1 and 15*** (total dose per cycle 1000 mg/m²)
	4 weeks[97,98]***:***	***1000 mg/m² IV over 24 hours for 4 consecutive days*** starting on day 1 (total dose per cycle 4000 mg/m²)
	6 weeks[99,100]***:***	***400-500 mg/m² IV on day 1, 8, 15 and 22*** (total dose per cycle 1600-2000 mg/m²)
	6 weeks[100]***:***	***1000 mg/m² IV over 24 hours for 4 consecutive days*** starting on day 1 (total dose per cycle 4000 mg/m²)
Ocular (topical):	***4-6 weeks***[66]:	***1% eye drops (one drop) instilled in the affected eye 3 to 4 times daily for 4 to 5 consecutive days each week***
	4 weeks[11,36,66]:	***1% eye drops (one drop) instilled in the affected eye 4 times daily for 7 consecutive days*** starting on day 1, followed by 21 days of no treatment
	28-30 days[36,37]:	1% eye drops (one drop) instilled in the affected eye 3 to 4 times daily for 28-30 consecutive days starting on day 1, followed by 28-30 days of no treatment
	2-3 weeks[101]:	1% eye drops (one drop) instilled in the affected eye 3 to 4 times daily for 14-21 consecutive days starting on day 1, followed by 3-10 weeks of no treatment
	30-49 days[36,37,102]:	1% eye drops (one drop) instilled in the affected eye 4 times daily for 2-4 days starting on day 1, followed by 30-45 days of no treatment (pulse therapy)
Concurrent radiation[103-110]*:*	can be used with variable schedules and dosing; specific treatment protocols must be consulted; see Special Precautions regarding patients who have received high-dose pelvic radiation	
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	

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

Dosage in obesity[9]*:*	if patient is obese or there has been a spurious weight gain because of edema, ascites or other form of abnormal fluid retention, the ideal weight or estimated lean body mass should be used
Dosage in renal failure:	no adjustment required
Dosage in hepatic failure[111-115]:	standard doses have been used in some patients with elevated bilirubin; may consider 50% dose reduction for starting doses or omit dose for bilirubin >85 micromol/L or AST >180 units/L
Dosage in dialysis:	hemodialysis: give ½ dose[7]; administer dose following hemodialysis[10] chronic ambulatory peritoneal dialysis (CAPD): no data[7] continuous renal replacement therapy (CRRT): give full dose[116]
Topical[44]*:*	apply twice daily x 2-4 weeks

Children:

Intravenous[117]*:*	500 mg/m^2 IV once or daily x 5
	800-1200 mg/m^2 IV over 24-120 h
Topical[45]*:*	use and dose as determined by physician

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