Drug Monograph

A - Drug Name

fluorouracil

SYNONYM(S): 5-fluorouracil; 5-FU

COMMON TRADE NAME(S): Efudex® Cream; IV generic brands available

back to top

B - Mechanism of Action and Pharmacokinetics

Fluorouracil was developed based on the observation that some tumour cells utilized the base pair uracil for DNA synthesis more efficiently than did normal cells. It is a fluorinated pyrimidine antimetabolite that is metabolized intracellularly to its active form, fluorouridine monophosphate (FdUMP), which then inhibits DNA synthesis by inhibiting thymidylate synthetase and the normal production of thymidine. Effects on RNA (incorporation into RNA and RNA inhibition) also occur. Fluorouracil is cell cycle phase-specific (S-phase).

Absorption	Bioavailability	Topical: Insignificant (<5-10%)
Distribution	Into all body water by passive diffusion, crosses placenta, high and persistent levels in malignant effusions.	
	Cross blood brain barrier?	yes
	PPB	10 %
Metabolism	Activated in target cells, 80% of dose degraded in liver by dihydropyrimidine dehydrogenase (DPD).	
	Active metabolites	FdUMP, FdUTP, FUTP

	Inactive metabolites	yes
Elimination	60-80% excreted as respiratory CO_2, 2-3% by biliary system. Higher clearance occurs in IV infusions than IV injections, due to saturation of metabolic or transport processes at higher drug concentrations.	
	Urine	15-20% as intact drug within 6 hours.
	Half-life	6-20 minutes; dose-dependent.

back to top

C - Indications and Status

Health Canada Approvals:

- Breast cancer (adjuvant/palliative)
- Gastrointestinal cancer (adjuvant/palliative colorectal, gastric, pancreatic - palliative)
- Genitourinary cancer (bladder, prostate - palliative)
- Head and neck cancer (palliative)
- Gynecological (ovarian; palliative)
- Premalignant keratoses (topical)
- Superficial basal cell carcinoma (topical)

Other Uses:

- Gastrointestinal cancer (hepatobiliary, neuroendocrine tumours, small bowel and appendix, esophageal, anal)
- Genitourinary cancer (penile, renal cell)
- Gynecological cancer (vulvar)
- Primary unknown
- Skin (squamous cell)
- Lung (neuroendocrine)

back to top

D - Adverse Effects

Emetogenic Potential: Low (Bolus)
Minimal (CIV)

Extravasation Potential: Irritant

The following table lists side effect incidences reported from the fluorouracil arm (IV infusion on days 1 and 2) in a phase III study in advanced colorectal cancer patients. Incidences marked with "^" were reported from other sources, including severe adverse effects from other studies or post-marketing

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<10%) ^	I
	Arterial/venous thromboembolism (6%)	E
	Cardiotoxicity (<10%) ^	D
	ECG changes (69%) (asymptomatic; severe in rare cases)^	I
Dermatological	Alopecia (17%) (mild)	E
	Erythema (including necrosis, with topical application)	I E
	Hand-foot syndrome (13%)	E
	Nail disorder (occasional)	E
	Photosensitivity (occasional)	E
	Radiation recall reaction (rare)	I E
	Rash (20%) (extremities, sometimes on trunk) / dry skin (may be severe)	E
Gastrointestinal	Anorexia (19%)	E
	Diarrhea (45%) (6% severe)	E
	GI ulcer or bleeding (rare)	E
	Mucositis (29%) (3% severe)	E
	Nausea, vomiting (55%) (4% severe)	I
Hematological	Anemia (91%) (2% severe)	E
	Hemolysis (rare)	E
	Myelosuppression ± infection, bleeding (48%) (13% severe)	E
Hepatobiliary	↑ Bilirubin (36%) (11% severe)	D
	Hepatic necrosis (rare; may be fatal)	D
Hypersensitivity	Hypersensitivity (rare; including anaphylaxis)	I
Injection site	Vein discolouration (occasional)	I
Nervous	Ataxia / acute cerebellar syndrome (rare, reversible, but may	E D

System	persist following discontinuation of treatment)	
	Confusion	E D
	Extrapyramidal disorder or cortical dysfunction (rare; usually reversible)	E D
	Leukoencephalopathy (rare)	E D
	Optic neuritis , oculomotor disturbance (rare)	E D
Ophthalmic	Conjunctivitis (25%) and/or tearing^	I E
	Other - tear duct fibrosis (rare, reversible)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** 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 side effects for fluorouracil include ECG changes, nausea/vomiting, myelosuppression ± infection (including anemia), bleeding, diarrhea, ↑ bilirubin, mucositis, conjunctivitis, rash and anorexia.

Following longer IV infusions, ***mucositis, hand-foot syndrome and diarrhea*** occur most commonly. Diarrhea may be profuse and life-threatening following administration of leucovorin with fluorouracil. ***Leukopenia*** is the usual dose-limiting toxicity after IV bolus administration

Patients with dihydropyrimidine dehydrogenase deficiency (DPD) are at risk of severe life-threatening toxicity with fluorouracil. While severe deficiency is rare, 3-4% of the population has some degree of DPD deficiency. No dose has been proven safe for patients with complete absence of DPD activity.

Excessive lacrimation can occur. Transient blurring of vision, eye irritation and excessive **nasal discharge** have also been reported. The onset of eye symptoms may occur at any time during treatment. Fluorouracil has been demonstrated in tear fluid causing acute and chronic conjunctivitis that can lead to tear duct fibrosis.

Acute cerebellar syndrome is manifested as ataxia of the trunk or extremities, disturbance of gait and speech, coarse nystagmus and dizziness. The ataxia syndrome is related to peak plasma levels of the drug rather than to cumulative dose, and is therefore more common with bolus doses than with infusions. It usually resolves after treatment is discontinued, but may persist in some cases. **Leukoencephalopathy** has been reported with symptoms such as decreased alertness, agitation, and disorientation memory deficit. This usually resolves within a few days of discontinuing fluorouracil.

Palmar-plantar erythrodysesthesia or **hand-foot syndrome** has been noted with protracted and high dose continuous infusion. The syndrome begins with dysesthesias of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot. The syndrome resolves gradually over 5 to 7 days with cessation of drug infusion.

Cardiotoxicity has been reported and may be caused by coronary vasospasm, endothelial cell damage or increased thrombogenicity. It occurs in less than 10% of patients, of which up to 8% may be fatal. Cardiac effects include ECG changes, angina, arrhythmias, myocardial infarction, heart failure and are usually reported within 72 h of the first cycle of fluorouracil. Cardiotoxicity is independent of dose or underlying cardiac risk factors, but may be more common with infusions. Patients should be rechallenged only when there are no other treatment options.

Fluorouracil has the potential to enhance radiation injury to tissues. While often called **radiation recall reactions**, the timing of the radiation may be before, concurrent with or even after the administration of the fluorouracil. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

Hemolytic-uremic syndrome has been reported when used in combination with mitomycin C.

Topical use:

When applied to a lesion, the following occurs: Erythema, usually followed by vesiculation, erosion, ulceration, necrosis and epithelization. The lower frequency and intensity of activity in adjacent normal skin indicates a selective cytotoxic property. An occlusive dressing is not essential, and may increase the incidence of inflammatory reactions in adjacent normal skin. Therapy is usually continued to reach the erosion, necrosis and ulceration stage (2-4 weeks), after which healing occurs over 4-8 weeks. The most frequent local reactions are pain, pruritus, hyperpigmentation and burning at the application site. Avoid prolonged exposure to sunlight or ultraviolet light during treatment and 1-2 months after ending treatment as the intensity of the reaction may be increased.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with fluorouracil. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Consider a reduced starting dose for patients who are heavily pretreated, malnourished or have poor performance status, or in patients with large third space collections or edema.

Adults:

IV bolus:

- q4w: 425 mg/m^2 day x 5 days
- q4w: 500-600 mg/m^2 days 1 & 8

IV infusion:

- q3w: 200 mg/m^2/day on days 1-21 as continuous infusion
- q3-4w: 750-1000 mg/m^2/day x 4-5 days as continuous infusion
- q2w: 600 mg/m^2/day x 22 hours on days 1 and 2
- q2w: 2400 mg/m^2 over 46 hours starting on day 1

Topical:

- Twice daily: x 1-4 weeks. Stop when erosion evident, usually 2-4 weeks. Allow 1-2 months for healing. Total area treated at one time should not exceed 500 cm^2 (23x23 cm). Larger areas should be treated one section at a time.

Dosage with Toxicity:

Modify according to protocol by which patient is being treated.

Toxicity or Counts (x 10^9/L)	During Cycle	For Next cycle
Platelets < 80 or ANC < 1.5	Hold*	May consider ↓
Bleeding, febrile neutropenia	Hold*	↓ by 25%
≥ grade 3 GI	Hold*	↓ by 25%
≥ grade 3 Hand-Foot Syndrome	Hold*	↓ by 25%
CNS	Hold*	↓ by 25%
Cardiac	Hold*	Consider discontinuing
* Do not retreat until ANC ≥ 1.5 x 10^9/L , platelets ≥ 100 x 10^9/L and organ toxicity ≤ grade 2. With severe toxicity, consider testing for DPD deficiency prior to rechallenge.		

Dosage with Hepatic Impairment:

Consider dose reduction with moderate to severe hepatic impairment.

Suggested:

Bilirubin		**AST/ALT**	**Fluorouracil (% previous dose)**
< 2 x ULN	and	3-5 x ULN	75 %
2-4 x ULN	or	5-10 x ULN	50-75%
> 4 x ULN	or	> 10 x ULN	Discontinue

Dosage with Renal Impairment:

No adjustment required, although reduction may be considered with severe renal insufficiency.

Dosage in the elderly:

Elderly patients are at a higher risk of developing toxicities, likely due to lower bone marrow reserve.

back to top

F - Administration Guidelines

IV Push or Intermittent Infusion:

- Slow push through sidearm of free-flowing IV (5% Dextrose, Normal Saline)
- May be mixed in 50mL minibag (NS or D5W); infuse over 15 min.

- Store unopened vials at 15ºC to 25ºC. Protect from light.

IV Continuous Infusion:

- Refer to local guidelines on preparation of fluorouracil IV infusion for central or peripheral lines. A lower concentration is usually used for peripheral IV infusions to prevent vein irritation.
- Continuous infusion using CADD infusion pump, or similar device
- Infusion volume, duration and administration via central or peripheral line depend on the regimen used.
- If given peripherally, inspect peripheral infusion sites daily and replace if evidence of irritation or extravasation.
- Incompatible with doxorubicin, epirubicin, diazepam, methotrexate and cytarabine; line must be flushed between administrations of fluorouracil and these agents.
- Store at room temperature (15 to 25ºC). Protect from light.

Topical:

- Glove or non-metal applicator preferred. If fingertips used, wash hands immediately afterward.
- Exercise care when applying the cream near the eyes, nostrils and mouth.

Antidote for Fluorouracil Overdose:

Uridine triacetate is a prodrug of uridine and is a specific antidote for treating fluorouracil overdose or severe early onset toxicities. If available, consider administering as soon as possible (i.e. within 96 hours) for suspected overdose. If not available, treatment is symptomatic and supportive.

For usage approval and supply, contact Health Canada's Special Access Program (SAP) (Phone: 613-941-2108. On-call service is available for emergencies). Uridine triacetate (Vistogard®) is supplied by its manufacturer in the United States.

The recommended dosing and administration for **uridine triacetate** in patients ≥18 years is:

- 10 grams (1 packet of coated granules) orally every 6 hours for 20 doses in total, without regards to meals.
- Granules should not be chewed. They should be mixed with 3 to 4 ounces of soft foods such as applesauce, pudding or yogurt.
- The dose should be ingested within 30 minutes of preparation, followed by at least 4 ounces of water.
- Refer to the prescribing information on dose preparation for NG-tube or G-tube use.

Additional resources on the management of fluorouracil infusion overdose:

- Management of Fluorouracil Infusion Overdose Guideline (Alberta Health Services)
- Management of Fluorouracil Infusion Overdose at the BCCA - Interim Guidance (BC Cancer Agency)

back to top

G - Special Precautions

Contraindications:

- patients with poor nutritional state
- patients with depressed bone marrow function (prior pelvic irradiation / marrow infiltration)
- patients with potentially serious infections
- patients with known hypersensitivity to the drug or any of its excipients
- patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Fluorouracil should not be used within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues.

Other Warnings/Precautions:

- Use with extreme caution in patients who:
  - have undergone recent major surgery,
  - have renal or hepatic impairment,
  - have widespread bone marrow involvement,
  - have previous use of other myelosuppressive chemotherapeutic agents,
  - have a history of high dose irradiation to bone marrow-bearing areas,
  - have a history of heart disease,
  - or are suspected to have DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Avoid the use of live vaccines.

Other Drug Properties:

- Carcinogenicity: Probable

Pregnancy and Lactation:

- Mutagenicity: Yes
- Embryotoxicity: Yes
- Teratogenicity: Yes
- Crosses placental barrier: Yes
  Fluorouracil is contraindicated in pregnancy. Appropriate contraception should be used by both sexes during treatment, and for at least **6 months** after the last dose (generic recommendation).
- Breastfeeding: Contraindicated
- Fertility effects: Probable

back to top

H - Interactions

Laboratory tests for bilirubin (icteric index) and urinary 5-HIAA may increase or have false positive results. Increases in T3 and T4 levels have been reported in euthyroid, advanced breast cancer patients treated with single agent fluorouracil, and these changes were reversible within 4 weeks after the end of treatment.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Brivudine, sorivudine and chemically related analogues	Significant ↑ in 5-FU exposure and toxicities	Irreversible DPD inhibition	CONTRAINDICATED Use alternative antiviral therapy or allow at least 4 weeks washout period between brivudine/ sorivudine/ analogues and starting 5-FU treatment. Immediate hospitalization with measures to reduce 5-FU toxicity is recommended, in case of accidental use of nucleoside analogues that inhibit DPD in 5-FU treated patients .
mitomycin	↑ incidence of hemolytic-uremic syndrome with long-term usage	Unknown	Caution
cimetidine	↑ serum concentrations of fluorouracil; fatal cases have been reported	appears to interfere with fluorouracil metabolism (e.g. by inhibiting hepatic enzymes and reducing hepatic blood flow)	Caution; observe for increased toxicity of fluorouracil
leucovorin	↑ 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	↑ serum concentration and/or toxicity of fluorouracil; fatal cases have been	↓ clearance of fluorouracil	Avoid if possible

	reported		
phenytoin	↑ phenytoin levels and toxicity	Possible inhibition or decreased synthesis of CYP2C9 by fluorouracil	Monitor phenytoin levels and patient
Thiazide diuretics	↑ myelosuppression	↓ renal excretion of fluorouracil	Consider an alternative antihypertensive
warfarin	↑ effects of warfarin; fatal cases have been reported	↓ CYP2C9 enzymes for metabolism; reduced warfarin clearance	Monitor INR closely; adjust warfarin doses accordingly

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and before each cycle
Liver function tests	Baseline and before each cycle
Renal function tests	Baseline and before each cycle
Clinical assessment and grading of stomatitis, diarrhea, bleeding, infection, local site toxicity, skin effects (rash or hand-foot-syndrome), cardiovascular, ophthalmic effects, and neurotoxicity	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
INR in patients taking warfarin	Baseline and as clinically indicated

back to top

K - References

Budd GT, Fleming TR, Bukowski RM et al. 5-fluorouracil and folinic Acid in the treatment of metastatic colorectal cancer: a randomized comparison. A Southwest oncology group study. J Clin Oncol 1987;5:272-7.

Fluorouracil: ASHP's Interactive Handbook on Injectable Drugs.

Fluorouracil drug monograph Cancer Drug Manual. British Columbia Cancer Agency (BCCA). Accessed November 21, 2018.

Gradishar WJ, Vokes EE, et al. 5-Fluorouracil cardiotoxicity: A critical review. Annals of Oncology 1990;1: 409-14.

Griffin JD, Garnick MB. Eye toxicity of cancer chemotherapy: a review of the literature. Cancer 1981;48(7):1539-49.

Health Canada's Special Access Programs, Health Canada. Accessed May 26, 2021.

Management of Fluorouracil Infusion Overdose Guideline. Alberta Health Services, Feb 2016.

Management of Fluorouracil Infusion Overdose at the BCCA - Interim Guidance. BC Cancer Agency, May 2015.

McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 1074-8.

Prescribing Information: Uridine triacetate (Vistogard®). Wellstat Therapeutics (US), Feb 2017.

Product Monograph: Fluorouracil. Sandoz Canada, April 3, 2012.

Product Monograph: Fluorouracil. Biolyse Pharma Corp., March 7, 2018.

Product Monograph: Irinotecan. Pfizer Canada Inc., Feb 11, 2015.

Product Monograph: Efudex® (fluorouracil topical). Valeant Canada Limited. December 15, 2004.

Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. Expert Opin Drug Saf 2009; 8(2): 191-202

Sara JD, Kaur J, Kodhadadi R, et al. 5-fluorouracil and cardiotoxicity: a review. Ther Adv Med Oncol 2018;10:1-18.

Sorrentino MF, Kim J, Foderaro AE, et al. Fluorouracil induced cardiotoxicity: review of the literature. Cardiol J 2012;19(5):453-8.

Summary of Product Characteristics: Efudix®. Meda Pharmaceuticals (UK), March 2014.

April 2024 Removed previous manufacturer name from antidote information

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

While care has been taken in the preparation of the information contained in the Formulary, such information is provided on an “as-is” basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information’s quality, accuracy, currency, completeness, or reliability.

CCO and the Formulary’s content providers shall have no liability, whether direct, indirect, consequential, contingent, special, or incidental, related to or arising from the information in the Formulary or its use thereof, whether based on breach of contract or tort (including negligence), and even if advised of the possibility thereof. Anyone using the information in the Formulary does so at his or her own risk, and by using such information, agrees to indemnify CCO and its content providers from any and all liability, loss, damages, costs and expenses (including legal fees and expenses) arising from such person’s use of the information in the Formulary.

back to top