

## Fluorouracil (systemic): Drug information

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(For additional information [see "Fluorouracil \(systemic\): Patient drug information "](#) and [see "Fluorouracil \(systemic\): Pediatric drug information"](#))

For abbreviations and symbols that may be used in Lexicomp ([show table](#))

**Brand Names: US** Adrucil

**Brand Names: Canada** Fluorouracil Injection

**Pharmacologic Category** Antineoplastic Agent, Antimetabolite; Antineoplastic Agent, Antimetabolite (Pyrimidine Analog)

### Dosing: Adult

#### Breast cancer: IV:

*CEF or FEC regimen:* 500 mg/m<sup>2</sup> on days 1 and 8 every 28 days (in combination with cyclophosphamide and epirubicin) for 6 cycles (Levine 1998)

*CMF regimen:* 600 mg/m<sup>2</sup> on days 1 and 8 every 28 days (in combination with cyclophosphamide and methotrexate) for 6 cycles (Goldhirsch 1998; Levine 1998)

*CAF or FAC regimen (off-label dosing):* 500 mg/m<sup>2</sup> on days 1 and 8 every 21 to 28 days (in combination with cyclophosphamide and doxorubicin) for 6 cycles (Assikis 2003)

**Colorectal cancer:** IV: 400 mg/m<sup>2</sup> bolus on day 1, followed by 1,200 to 1,500 mg/m<sup>2</sup>/day continuous infusion for 2 days (over 46 hours) every 2 weeks (in combination with leucovorin ± either oxaliplatin or irinotecan) **or**

*Roswell Park regimen:* 500 mg/m<sup>2</sup> (bolus) on days 1, 8, 15, 22, 29, and 36 (1 hour after leucovorin) every 8 weeks (in combination with leucovorin) for 4 cycles (Haller 2005)

*FOLFOX6 and mFOLFOX6 regimen:* 400 mg/m<sup>2</sup> bolus on day 1, followed by 1200 mg/m<sup>2</sup>/day continuous infusion for 2 days (over 46 hours) every 2 weeks (in combination with leucovorin and oxaliplatin) until disease progression or unacceptable toxicity (Cheeseman 2002)

*FOLFIRI regimen:* 400 mg/m<sup>2</sup> bolus on day 1, followed by 1200 mg/m<sup>2</sup>/day continuous infusion for 2 days (over 46 hours) every 2 weeks (in combination with leucovorin and irinotecan) until disease progression or unacceptable toxicity; after 2 cycles, may increase continuous infusion fluorouracil dose to 1500 mg/m<sup>2</sup>/day (over 46 hours) (Andre 1999)

*FLOX regimen (off-label dosing) :* 500 mg/m<sup>2</sup> bolus on days 1, 8, 15, 22, 29, and 36 (1 hour after leucovorin) every 8 weeks (in combination with leucovorin and oxaliplatin) for 3 cycles (Kuebler 2007)

**Gastric cancer:** IV: 200 to 1,000 mg/m<sup>2</sup>/day as a continuous infusion over 24 hours (as part of a platinum-containing regimen); the duration and frequency of each cycle varies based on the dose and regimen.

*CF regimen:* 1,000 mg/m<sup>2</sup>/day continuous infusion days 1 to 4 and days 29 to 32 of a 35-day treatment cycle (preoperative chemoradiation; in combination with cisplatin) (Tepper 2008)

*ECF regimen (resectable disease):* 200 mg/m<sup>2</sup>/day continuous infusion days 1 to 21 every 3 weeks (in combination with epirubicin and cisplatin) for 6 cycles (3 cycles preoperatively and 3 cycles postoperatively) (Cunningham 2006)

*ECF or EOF regimen (advanced disease):* 200 mg/m<sup>2</sup>/day continuous infusion days 1 to 21 every 3 weeks (in combination with epirubicin and either cisplatin or oxaliplatin) for a planned duration of 24 weeks (Sumpter 2005)

*TCF or DCF regimen:* 750 mg/m<sup>2</sup>/day continuous infusion days 1 to 5 every 3 weeks or 1000 mg/m<sup>2</sup>/day continuous infusion days 1 to 5 every 4 weeks (in combination with docetaxel and cisplatin) until disease progression or unacceptable toxicity (Ajani 2007; Van Cutsem 2006)

*ToGA regimen (HER2-positive):* 800 mg/m<sup>2</sup>/day continuous infusion days 1 to 5 every 3 weeks (in combination with cisplatin and trastuzumab) until disease progression or unacceptable toxicity (Bang 2010)

**Pancreatic cancer: IV:**

*FOLFIRINOX regimen:* 400 mg/m<sup>2</sup> bolus on day 1, followed by 1,200 mg/m<sup>2</sup>/day continuous infusion for 2 days (over 46 hours) every 14 days (in combination with leucovorin, irinotecan, and oxaliplatin) until disease progression or unacceptable toxicity for a recommended 12 cycles (Conroy 2011)

*Chemoradiation therapy (off-label dosing):* 250 mg/m<sup>2</sup>/day continuous infusion for 3 weeks prior to and then throughout radiation therapy (Regine 2008)

*Fluorouracil-Leucovorin (off-label dosing):* 425 mg/m<sup>2</sup>/day (bolus) days 1 to 5 every 28 days (in combination with leucovorin) for 6 cycles (Neoptolemos 2010)

**Anal carcinoma (off-label use):** IV: 1,000 mg/m<sup>2</sup>/day continuous infusion days 1 to 4 and days 29 to 32 (in combination with mitomycin and radiation therapy) (Ajani 2008; Flam 1996)

**Bladder cancer (off-label use):** IV: 500 mg/m<sup>2</sup>/day continuous infusion days 1 to 5 and days 16 to 20 (in combination with mitomycin and radiation therapy) (James 2012)

**Cervical cancer (off-label use):** IV: 1,000 mg/m<sup>2</sup>/day continuous infusion days 1 to 4 (in combination with cisplatin and radiation therapy) every 3 weeks for 3 cycles (Eifel 2004; Morris 1999)

**Esophageal cancer (off-label use):** IV:

*CF regimen:* 1,000 mg/m<sup>2</sup>/day continuous infusion days 1 to 4 and days 29 to 32 of a 35-day treatment cycle (preoperative chemoradiation; in combination with cisplatin) (Tepper 2008)

*ECF regimen (resectable disease):* 200 mg/m<sup>2</sup>/day continuous infusion days 1 to 21 every 3 weeks (in combination with epirubicin and cisplatin) for 6 cycles (3 cycles preoperatively and 3 cycles postoperatively) (Cunningham 2006)

*ECF or EOF regimen (advanced disease):* 200 mg/m<sup>2</sup>/day continuous infusion days 1 to 21 every 3 weeks (in combination with epirubicin and either cisplatin or oxaliplatin) for a planned duration of 24 weeks (Sumpter 2005)

*MCF regimen:* 300 mg/m<sup>2</sup>/day continuous infusion for up to 6 months (in combination with mitomycin and cisplatin) (Ross 2002)

*TCF or DCF regimen:* 750 mg/m<sup>2</sup>/day continuous infusion days 1 to 5 every 3 to 4 weeks (in combination with docetaxel and cisplatin) until disease progression or unacceptable toxicity (Ajani 2007; Van Cutsem 2006)

**Head and neck cancer, squamous cell (off-label use):** IV:

*Platinum-Fluorouracil (CF) regimen:* 1,000 mg/m<sup>2</sup>/day continuous infusion days 1 to 4 every 3 weeks (in combination with cisplatin) for at least 6 cycles (Gibson 2005) **or** 1,000 mg/m<sup>2</sup>/day continuous infusion days 1 to 4 every 4 weeks (in combination with carboplatin) for at least 6 cycles (Forastiere 1992) **or** 600 mg/m<sup>2</sup>/day continuous infusion days 1 to 4, 22 to 25, and 43 to 46 (in combination with carboplatin and radiation) (Bourhis 2012; Denis 2004)

*TPF regimen:* 1,000 mg/m<sup>2</sup>/day continuous infusion days 1 to 4 every 3 weeks (in combination with docetaxel and cisplatin) for 3 cycles, and followed by chemoradiotherapy (Posner 2007) **or** 750 mg/m<sup>2</sup>/day continuous infusion days 1 to 5 every 3 weeks (in combination with docetaxel and cisplatin) for up to 4 cycles, followed by radiation in patients without progressive disease (Vermorken 2007)

*Platinum, 5-FU, and cetuximab regimen:* 1,000 mg/m<sup>2</sup>/day continuous infusion days 1 to 4 every 3 weeks (in combination with cetuximab and either cisplatin or carboplatin) for a total of up to 6 cycles (Vermorken 2008)

**Hepatobiliary cancer (off-label use):** IV: 600 mg/m<sup>2</sup> (bolus) on days 1, 8, and 15 every 4 weeks (in combination with gemcitabine and leucovorin) (Alberts 2005). Additional data may be needed to further define the role of fluorouracil in this condition.

**Neuroendocrine tumors, pancreatic (off-label use):** IV: 400 mg/m<sup>2</sup>/day (bolus) days 1 to 5 every 28 days (in combination with doxorubicin and streptozocin) for at least 4 cycles (Kouvaraki 2004). Additional data may be necessary to further define the role of fluorouracil in the management of this condition.

**Penile cancer, advanced, squamous cell (off-label use):** IV: 800 to 1,000 mg/m<sup>2</sup>/day continuous infusion for 4 days every 21 days (in combination with cisplatin) (Di Lorenzo 2012). Additional data may be needed to further define the role of fluorouracil in this condition.

**Unknown primary cancer, squamous cell (off-label use):** IV: 750 mg/m<sup>2</sup>/day continuous infusion for 5 days every 21 days (in combination with docetaxel and cisplatin) for 3 cycles (Pointreau 2009) **or** 500 mg/m<sup>2</sup>/day continuous infusion for 5 days every 21 days (in combination with paclitaxel and cisplatin) for 3 cycles (Hitt 2005) **or** 400 mg/m<sup>2</sup>/day (bolus) followed by 1,200 mg/m<sup>2</sup>/day continuous infusion for 2 days (over 46 hours) every 2 weeks (in combination with leucovorin and oxaliplatin) (Cheeseman 2002) **or** 700 mg/m<sup>2</sup>/day continuous infusion for 5 days (in combination with cisplatin) every 28 days until disease progression or unacceptable toxicity (Kusaba 2007). Additional data may be needed to further define the role of fluorouracil in this condition.

**Vulvar cancer, advanced (off-label use):** IV: 750 mg/m<sup>2</sup>/day continuous infusion days 1 to 5 every 14 days for 2 cycles (in combination with concomitant radiation and mitomycin) (Landoni 1996). Additional

data may be needed to further define the role of fluorouracil in this condition.

## Dosing: Pediatric

(For additional information [see "Fluorouracil \(systemic\): Pediatric drug information"](#))

**Nasopharyngeal carcinoma (off-label use):** Children  $\geq 8$  years and Adolescents: IV: 1,000 mg/m<sup>2</sup>/day continuous infusion for 3 or 5 days every 3 or 4 weeks (in combination with cisplatin with or without either methotrexate or leucovorin, followed by radiation therapy [ $\pm$  interferon beta]) for 3 or 4 cycles (Buehrlen 2012; Casanova 2012; Mertens 2005; Rodriguez-Galindo 2005). Additional data may be needed to further define the role of fluorouracil in this condition.

**Dosing: Geriatric** Refer to adult dosing.

**Dosing: Renal Impairment** There are no dosage adjustments provided in the manufacturer's labeling; use with caution. The following adjustments have been suggested:

CrCl  $< 50$  mL/minute and continuous renal replacement therapy (CRRT): No dosage adjustment necessary (Aronoff 2007).

Hemodialysis:

Administer standard dose following hemodialysis on dialysis days (Janus 2010).

Administer 50% of standard dose following hemodialysis (Aronoff 2007).

**Dosing: Hepatic Impairment** There are no dosage adjustments provided in the manufacturer's labeling; use with caution. The following adjustments have been suggested:

Bilirubin  $> 5$  mg/dL: Avoid use (Floyd 2006).

Hepatic impairment (degree not specified): Administer  $< 50\%$  of dose, then increase if toxicity does not occur (Koren 1992).

**Dosing: Obesity** *ASCO Guidelines for appropriate chemotherapy dosing in obese adults with cancer:* Utilize patient's actual body weight (full weight) for calculation of body surface area- or weight-based dosing, particularly when the intent of therapy is curative; manage regimen-related toxicities in the same manner as for nonobese patients; if a dose reduction is utilized due to toxicity, consider resumption of full weight-based dosing with subsequent cycles, especially if cause of toxicity (eg, hepatic or renal impairment) is resolved (Griggs 2012).

## Dosing: Adjustment for Toxicity

Withhold treatment for the following (may resume at a reduced dose following resolution or improvement to grade 1):

Dermatologic toxicity: Grade 2 or 3 palmar-plantar erythrodysesthesia (hand-foot syndrome)

Gastrointestinal toxicity: Grade 3 or 4 diarrhea; grade 3 or 4 mucositis

Hematologic toxicity: Grade 4 myelosuppression

Withhold treatment for the following (there is no recommended dose for resumption):

Cardiovascular toxicity: Angina, MI/ischemia, arrhythmia, or heart failure in patients without a history of coronary artery disease or myocardial dysfunction

CNS toxicity: Acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances

Hyperammonemic encephalopathy

**Dosage Forms** Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous:

Adrucil: 500 mg/10 mL (10 mL); 2.5 g/50 mL (50 mL); 5 g/100 mL (100 mL)

Generic: 500 mg/10 mL (10 mL); 1 g/20 mL (20 mL); 2.5 g/50 mL (50 mL); 5 g/100 mL (100 mL)

Solution, Intravenous [preservative free]:

Generic: 2.5 g/50 mL (50 mL); 5 g/100 mL (100 mL)

**Generic Equivalent Available (US)** Yes

**Administration** IV administration rate varies by protocol; refer to specific reference for protocol. May be administered by IV push, IV bolus, or as a continuous infusion. Avoid extravasation (may be an irritant).

## **Hazardous Drugs Handling Considerations**

Hazardous agent (NIOSH 2016 [group 1]).

Use appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage.

NIOSH recommends double gloving, a protective gown, ventilated engineering controls (a class II biological safety cabinet or a compounding aseptic containment isolator), and closed system transfer devices (CSTDs) for preparation. Double gloving, a gown, and (if dosage form allows) CSTDs are required during administration (NIOSH 2016).

## **Use**

**Breast cancer:** Management of breast cancer

**Colon and rectal cancer:** Management of colon and rectal cancer

**Gastric cancer:** Management of stomach (gastric) cancer

**Pancreatic cancer:** Management of pancreatic cancer

## **Use: Off-Label**

Anal carcinoma; Bladder cancer; Cervical cancer; Esophageal cancer, advanced; Head and neck cancer; Hepatobiliary cancers (advanced); Nasopharyngeal carcinoma (pediatric); Neuroendocrine tumors (pancreatic); Penile cancer (advanced) (squamous cell); Unknown primary cancer (squamous cell); Vulvar cancer, advanced

## Medication Safety Issues

### Sound-alike/look-alike issues:

Fluorouracil may be confused with floxuridine, flucytosine

### High alert medication:

This medication is in a class the Institute for Safe Medication Practices (ISMP) includes among its list of drug classes which have a heightened risk of causing significant patient harm when used in error.

### Administration issues:

Continuous infusion: Serious errors have occurred when doses administered by continuous ambulatory infusion pumps have inadvertently been given over 1 to 4 hours instead of the intended extended continuous infusion duration. Depending on protocol, infusion duration may range from 46 hours to 7 days for fluorouracil continuous infusions. Ambulatory pumps utilized for continuous infusions should have safeguards to allow for detection of programming errors. If using an elastomeric device for ambulatory continuous infusion, carefully select the device and double check the flow rate. Appropriate prescribing (in single daily doses [not course doses] with instructions to infuse over a specific time period), appropriate training/certification/education of staff involved with dispensing and administration processes, and independent double checks should be utilized throughout dispensing and administration procedures.

**Adverse Reactions** Frequency not defined. Toxicity depends on duration of treatment and/or rate of administration.

Cardiovascular: Angina pectoris, cardiac arrhythmia, cardiac failure, cerebrovascular accident, ischemic heart disease, local thrombophlebitis, myocardial infarction, vasospasm, ventricular ectopy

Central nervous system: Cerebellar syndrome (acute), confusion, disorientation, euphoria, headache

Dermatologic: Alopecia, changes in nails (including nail loss), dermatitis, hyperpigmentation (supravenous), maculopapular rash (pruritic), palmar-plantar erythrodysesthesia, skin fissure, skin photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, xeroderma

Gastrointestinal: Anorexia, diarrhea, esophagopharyngitis, gastrointestinal hemorrhage, gastrointestinal ulcer, mesenteric ischemia (acute), nausea, stomatitis, tissue sloughing (gastrointestinal), vomiting

Hematologic & oncologic: Agranulocytosis, anemia, leukopenia (nadir: days 9 to 14; recovery by day 30), pancytopenia, thrombocytopenia

Hypersensitivity: Anaphylaxis, hypersensitivity reaction (generalized)

Ophthalmic: Lacrimal stenosis, lacrimation, nystagmus, photophobia, visual disturbance

Respiratory: Epistaxis

<1%, postmarketing, and/or case reports: Dysgeusia (Syed 2016)

**Contraindications** There are no contraindications listed in the manufacturer's US labeling.

*Canadian labeling:* Known hypersensitivity to fluorouracil or any component of the formulation; debilitated patients; poor nutritional state; depressed bone marrow function following radiotherapy or therapy with other antineoplastic agents; potentially serious infections.

## Warnings/Precautions

### **Concerns related to adverse effects:**

- Bone marrow suppression: Fluorouracil can cause severe and fatal hematologic toxicity (neutropenia, thrombocytopenia, and anemia). The neutrophil nadir usually occurs between 9 to 14 days after administration. Monitor blood counts prior to each treatment cycle, weekly if administered on a weekly or similar schedule, and as clinically indicated. Withhold fluorouracil for grade 4 hematologic toxicity; when blood counts resolve to grade 1 or lower, resume at a reduced dose.
- Cardiotoxicity: Based on postmarketing reports, fluorouracil may cause cardiotoxicity (angina, MI/ischemia, arrhythmia, and heart failure). Risk factors for cardiotoxicity include continuous infusion administration (versus IV bolus) and coronary artery disease. Withhold fluorouracil for cardiotoxicity. The risks of resuming fluorouracil in patients with resolved cardiotoxicity have not been established. In a scientific statement from the AHA, fluorouracil has been determined to be an agent that may either cause reversible direct myocardial toxicity or exacerbate underlying myocardial dysfunction (magnitude: moderate/major) (AHA [Page 2016]).
- GI toxicity: Fluorouracil is associated with severe diarrhea. Withhold treatment for grade 3 or 4 diarrhea until resolved or to grade 1 or lower, then resume fluorouracil at a reduced dose. Administer fluids, electrolyte replacement, and/or antidiarrheal treatments as necessary. Mucositis, stomatitis, or esophagopharyngitis (which may lead to mucosal sloughing or ulceration) may occur with fluorouracil. The incidence of mucositis is reported to be higher with IV bolus fluorouracil administration (vs continuous infusion). Withhold fluorouracil grade 3 or 4 mucositis; resume at a reduced dose once mucositis has resolved to grade 1 or lower.
- Hand-foot syndrome: Fluorouracil is associated with palmar-plantar erythrodysesthesia (hand-foot syndrome; HFS). Symptoms of HFS include a tingling sensation, pain, swelling, erythema with tenderness, and desquamation. HFS occurs more commonly when fluorouracil is administered as a continuous infusion (compared to IV bolus) and has been reported to occur more frequently in patients with prior chemotherapy exposure. The onset of HFS is usually after 8 to 9 weeks of fluorouracil, although may occur earlier. Initiate supportive care for symptomatic relief of HFS. Withhold fluorouracil for grade 2 or 3 HFS; resume at a reduced dose when HFS has resolved to grade 1 or lower.
- Hyperammonemic encephalopathy: Fluorouracil may result in hyperammonemic encephalopathy in the absence of liver disease or other identifiable cause (postmarketing reports). The onset of hyperammonemic encephalopathy signs/symptoms (altered mental status, confusion, disorientation,

coma, or ataxia, in the presence of concomitant elevated serum ammonia level) was within 72 hours after fluorouracil infusion initiation. Withhold fluorouracil for hyperammonemic encephalopathy and initiate ammonia-lowering therapy. The risks of resuming fluorouracil in patients with resolved hyperammonemic encephalopathy have not been established.

- Neurotoxicity: Fluorouracil may cause neurologic toxicity, including acute cerebellar syndrome and other neurologic events (postmarketing reports). Neurologic symptoms included confusion, disorientation, ataxia, or visual disturbances. Withhold fluorouracil for neurologic toxicity. There are insufficient data on the risks of resuming fluorouracil in patients with resolved neurologic toxicity.

#### ***Disease-related concerns:***

- Dihydropyrimidine dehydrogenase deficiency: Patients with select homozygous or compound heterozygous dihydropyrimidine dehydrogenase (DPD) gene mutations that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions (eg, mucositis, diarrhea, neutropenia, neurotoxicity) due to fluorouracil. Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions when administered fluorouracil. Based on clinical assessment of toxicity onset, duration, and severity, withhold or permanently discontinue fluorouracil in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. There is no fluorouracil dose that has been proven safe in patients with complete absence of DPD activity and data are insufficient to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

#### ***Concurrent drug therapy issues:***

- Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.
- Warfarin: Clinically significant coagulation parameter elevations have been reported with concomitant use of warfarin and fluorouracil. Closely monitor INR and prothrombin time in patients receiving concomitant coumarin-derivative anticoagulants such as warfarin and adjust the anticoagulant dose accordingly.

#### ***Other warnings/precautions:***

- Administration safety issues: Serious errors have occurred when doses administered by continuous ambulatory infusion pumps have inadvertently been given over 1 to 4 hours instead of the intended extended continuous infusion duration. Depending on protocol, infusion duration may range from 46 hours to 7 days for fluorouracil continuous infusions. Ambulatory pumps utilized for continuous infusions should have safeguards to allow for detection of programming errors. If using an elastomeric device for ambulatory continuous infusion, carefully select the device and double check the flow rate. Appropriate prescribing (in single daily doses [not course doses] with instructions to infuse over a specific time period), appropriate training/certification/education of staff involved with dispensing and administration processes, and independent double checks should be utilized throughout dispensing and administration procedures (ISMP [Smetzer 2015]).
- Antidote: Uridine triacetate (formerly called vistonuridine), has been studied in cases of fluorouracil overdose. In a clinical study of 98 patients who received uridine triacetate for fluorouracil toxicity (due to overdose, accidental capecitabine ingestion, or possible DPD deficiency), 96 patients recovered fully (Bamat 2013). Of 17 patients receiving uridine triacetate beginning within 8 to 96



hours after fluorouracil overdose, all patients fully recovered (von Borstel 2009). Refer to Uridine Triacetate monograph.

## **Metabolism/Transport Effects** Inhibits CYP2C9 (strong)

### **Drug Interactions**

(For additional information: [Launch drug interactions program](#)) Lexicomp®

Alitretinoin (Systemic): CYP2C9 Inhibitors (Strong) may increase the serum concentration of Alitretinoin (Systemic). Management: Consider reducing the alitretinoin dose to 10 mg when used together with strong CYP2C9 inhibitors. Monitor for increased alitretinoin effects/toxicities if combined with a strong CYP2C9 inhibitor. *Risk D: Consider therapy modification*

BCG (Intravesical): Immunosuppressants may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG (Intravesical): Myelosuppressive Agents may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

Bosentan: CYP2C9 Inhibitors (Strong) may increase the serum concentration of Bosentan. Management: Concomitant use of both a CYP2C9 inhibitor and a CYP3A inhibitor or a single agent that inhibits both enzymes with bosentan is likely to cause a large increase in serum concentrations of bosentan and is not recommended. See monograph for details. *Risk C: Monitor therapy*

Cannabis: CYP2C9 Inhibitors (Strong) may increase the serum concentration of Cannabis. More specifically, tetrahydrocannabinol serum concentrations may be increased. *Risk C: Monitor therapy*

Carvedilol: CYP2C9 Inhibitors (Strong) may increase the serum concentration of Carvedilol. Specifically, concentrations of the S-carvedilol enantiomer may be increased. *Risk C: Monitor therapy*

Cimetidine: May increase the serum concentration of Fluorouracil (Systemic). *Risk C: Monitor therapy*

CloZAPine: Myelosuppressive Agents may enhance the adverse/toxic effect of CloZAPine. Specifically, the risk for neutropenia may be increased. *Risk C: Monitor therapy*

Coccidioides immitis Skin Test: Immunosuppressants may diminish the diagnostic effect of Coccidioides immitis Skin Test. *Risk C: Monitor therapy*

CYP2C9 Substrates: CYP2C9 Inhibitors (Strong) may decrease the metabolism of CYP2C9 Substrates. *Risk D: Consider therapy modification*

Deferiprone: Myelosuppressive Agents may enhance the neutropenic effect of Deferiprone. *Risk X: Avoid combination*

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. *Risk C: Monitor therapy*

Diclofenac (Systemic): CYP2C9 Inhibitors (Strong) may increase the serum concentration of Diclofenac (Systemic). Management: Consider using a lower dose of diclofenac when used together with a strong CYP2C9 inhibitor. Arthrotec (diclofenac and misoprostol) labeling specifically recommends limiting the total daily dose to a maximum of 50 mg twice/day. *Risk D: Consider therapy modification*

Dipyrrone: May enhance the adverse/toxic effect of Myelosuppressive Agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased *Risk X: Avoid combination*

Dronabinol: CYP2C9 Inhibitors (Strong) may increase the serum concentration of Dronabinol. *Risk C: Monitor therapy*

Echinacea: May diminish the therapeutic effect of Immunosuppressants. *Risk D: Consider therapy modification*

Fingolimod: Immunosuppressants may enhance the immunosuppressive effect of Fingolimod. Management: Avoid the concomitant use of fingolimod and other immunosuppressants when possible. If combined, monitor patients closely for additive immunosuppressant effects (eg, infections). *Risk D: Consider therapy modification*

Fosphenytoin: Fluorouracil (Systemic) may increase the serum concentration of Fosphenytoin. *Risk D: Consider therapy modification*

Gemcitabine: May increase the serum concentration of Fluorouracil (Systemic). *Risk C: Monitor therapy*

Gimeracil: May increase the serum concentration of Fluorouracil (Systemic). *Risk X: Avoid combination*

Highest Risk QTc-Prolonging Agents: QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying) may enhance the QTc-prolonging effect of Highest Risk QTc-Prolonging Agents. Management: Avoid such combinations when possible. Use should be accompanied by close monitoring for evidence of QT prolongation or other alterations of cardiac rhythm. *Risk D: Consider therapy modification*

Lacosamide: CYP2C9 Inhibitors (Strong) may increase the serum concentration of Lacosamide. *Risk C: Monitor therapy*

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. *Risk D: Consider therapy modification*

Lenograstim: Antineoplastic Agents may diminish the therapeutic effect of Lenograstim. *Risk D: Consider therapy modification*

Leucovorin Calcium-Levoleucovorin: May enhance the adverse/toxic effect of Fluorouracil (Systemic). This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. *Risk C: Monitor therapy*

MetroNIDAZOLE (Systemic): May increase the serum concentration of Fluorouracil (Systemic). *Risk C: Monitor therapy*

MiFEPRIStone: May enhance the QTc-prolonging effect of QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying). Management: Though the drugs listed here have uncertain QT-prolonging effects, they all have some possible association with QT prolongation and should generally be avoided when possible. *Risk D: Consider therapy modification*

Moderate Risk QTc-Prolonging Agents: QTc-Prolonging Agents (Indeterminate Risk and Risk Modifying) may enhance the QTc-prolonging effect of Moderate Risk QTc-Prolonging Agents. *Risk C: Monitor therapy*

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. *Risk X: Avoid combination*

Nivolumab: Immunosuppressants may diminish the therapeutic effect of Nivolumab. *Risk D: Consider therapy modification*

Ocrelizumab: May enhance the immunosuppressive effect of Immunosuppressants. *Risk C: Monitor therapy*

Ospemifene: CYP2C9 Inhibitors (Strong) may increase the serum concentration of Ospemifene. *Risk C: Monitor therapy*

Palifermin: May enhance the adverse/toxic effect of Antineoplastic Agents. Specifically, the duration and severity of oral mucositis may be increased. Management: Do not administer palifermin within 24 hours before, during infusion of, or within 24 hours after administration of myelotoxic chemotherapy. *Risk D: Consider therapy modification*

Parecoxib: CYP2C9 Inhibitors (Strong) may increase the serum concentration of Parecoxib. *Risk C: Monitor therapy*

Phenytoin: Fluorouracil (Systemic) may increase the serum concentration of Phenytoin. *Risk D: Consider therapy modification*

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Promazine: May enhance the myelosuppressive effect of Myelosuppressive Agents. *Risk C: Monitor therapy*

Ramelteon: CYP2C9 Inhibitors (Strong) may increase the serum concentration of Ramelteon. *Risk C: Monitor therapy*

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. *Risk D: Consider therapy modification*

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. *Risk C: Monitor therapy*

SORafenib: May decrease the serum concentration of Fluorouracil (Systemic). SORafenib may increase the serum concentration of Fluorouracil (Systemic). *Risk C: Monitor therapy*

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. *Risk X: Avoid combination*

Tertomotide: Immunosuppressants may diminish the therapeutic effect of Tertomotide. *Risk C: Monitor therapy*

Tetrahydrocannabinol: CYP2C9 Inhibitors (Strong) may increase the serum concentration of Tetrahydrocannabinol. *Risk C: Monitor therapy*

Tofacitinib: Immunosuppressants may enhance the immunosuppressive effect of Tofacitinib. Management: Concurrent use with antirheumatic doses of methotrexate or nonbiologic disease modifying antirheumatic drugs (DMARDs) is permitted, and this warning seems particularly focused on more potent immunosuppressants. *Risk X: Avoid combination*

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. *Risk C: Monitor therapy*

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Management: Vaccine efficacy may be reduced. Complete all age-appropriate vaccinations at least 2 weeks prior to starting an immunosuppressant. If vaccinated during immunosuppressant therapy, revaccinate at least 3 months after immunosuppressant discontinuation. *Risk D: Consider therapy modification*

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants. *Risk X: Avoid combination*

Vitamin K Antagonists (eg, warfarin): Fluorouracil (Systemic) may increase the serum concentration of Vitamin K Antagonists. *Risk D: Consider therapy modification*

## **Pregnancy Risk Factor** D ([show table](#))

**Pregnancy Implications** Adverse effects (increased resorptions, embryoletality, and teratogenicity) have been observed in animal reproduction studies. Based on the mechanism of action, fluorouracil may cause fetal harm if administered during pregnancy (according to the manufacturer's labeling). Females of reproductive potential and male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following cessation of fluorouracil therapy.

Chemotherapy, if indicated, may be administered to pregnant women with breast cancer as part of a combination chemotherapy regimen (common regimens administered during pregnancy include doxorubicin [or epirubicin], cyclophosphamide, and fluorouracil); chemotherapy should not be administered during the first trimester, after 35 weeks' gestation, or within 3 weeks of planned delivery (Amant 2010; Loibl 2006). The European Society for Medical Oncology has published guidelines for diagnosis, treatment, and follow-up of cancer during pregnancy. The guidelines recommend referral to a facility with expertise in cancer during pregnancy and encourage a multidisciplinary team (obstetrician, neonatologist, oncology team). In general, if chemotherapy is indicated, it should be avoided during in the first trimester, there should be a 3-week time period between the last chemotherapy dose and anticipated delivery, and chemotherapy should not be administered beyond week 33 of gestation (Peccatori 2013).

Fertility (male and female) may be impaired during fluorouracil treatment.

**Breast-Feeding Considerations** It is not known if fluorouracil is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends a decision be made to discontinue breastfeeding or to discontinue fluorouracil, taking into account the importance of treatment to the mother.

**Dietary Considerations** Increase dietary intake of thiamine.

**Monitoring Parameters** CBC with differential and platelet count (prior to each treatment cycle, weekly if administered on a weekly or similar schedule, and as clinically indicated), renal function tests, LFTs, INR, and prothrombin time (in patients receiving concomitant coumarin-derivative anticoagulants); signs/symptoms of palmar-plantar erythrodysesthesia syndrome, cardiotoxicity, CNS toxicity, stomatitis,

diarrhea, and hyperammonemic encephalopathy.

**Mechanism of Action** A pyrimidine analog antimetabolite that interferes with DNA and RNA synthesis; after activation, F-UMP (an active metabolite) is incorporated into RNA to replace uracil and inhibit cell growth; the active metabolite F-dUMP, inhibits thymidylate synthetase, depleting thymidine triphosphate (a necessary component of DNA synthesis).

## Pharmacodynamics/Kinetics

**Distribution:** Fluorouracil distributes throughout the body, including brain tissue, CSF, bone marrow, intestinal mucosa, and liver.

**Metabolism:** Hepatic; via a dehydrogenase enzyme; FU must be metabolized to form active metabolites, 5-fluoroxymuridine monophosphate (F-UMP) and 5-fluoro-2'-deoxyuridine-5'-O-monophosphate (F-dUMP)

**Half-life elimination:** Following bolus infusion: 8 to 20 minutes

**Excretion:** Urine (5% to 20% as unchanged drug within 6 hours; metabolites over 3 to 4 hours)

## Pricing: US

### **Solution** (Aducil Intravenous)

2.5 gm/50 mL (50 mL): \$23.28

5 g/100 mL (100 mL): \$39.96

500 mg/10 mL (10 mL): \$6.66

### **Solution** (Fluorouracil Intravenous)

1 g/20 mL (20 mL): \$6.48

2.5 gm/50 mL (50 mL): \$15.42

5 g/100 mL (100 mL): \$30.84

500 mg/10 mL (10 mL): \$3.00

**Disclaimer:** The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly.

**International Brand Names** 5-Fluril (BD); 5-FU (DE, JP, KR); Agicil (MT); Curacil (ID); Fivoflu (IN, JO, PH, VE, ZW); Flonida (IN); Fluonco (PH); Flurablastin (DK, FI, NO, SE); Fluracedyl (BE, MY, NL, PH); Fluroblastin (VE); Fluroblastine (BE); Fluroxan (BD); Ftorolik (UA); Fu Ke (CN); La-Fu (CZ); Pharmauracil (PK); Ribofluor (DE); Sinofuan Implant (CN); Triosules (AR); Utoral (PH)

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