

# Management of 5FU (5-Fluorouracil) Infusion Overdose

Effective Date: September, 2022



## Background

Fluorouracil is commonly used alone or in combination for treating solid tumours. It is usually dosed at its maximum tolerated dose via intravenous injection or infusion. Mild toxicities to life-threatening events may occur with fluorouracil administration at greater than the intended dose or dose interval. This may occur due to errors in infusion pump programming, dose miscalculations, or device malfunction. There is currently no standard definition of fluorouracil infusion overdose. Toxicities can include but are not limited to myelosuppression, mucositis, diarrhea, nausea/vomiting, esophagitis and gastritis<sup>2</sup>. Less common but potentially severe events can include cardiogenic shock, gastrointestinal bleeding and perforation<sup>3</sup>. For further information on fluorouracil, please refer to [AHS Provincial Parenteral Monograph on Fluorouracil](#) and/or the BCCA [Parental Drug Information guide](#).

Fluorouracil infusions may be prescribed to infuse over multiple days at home via an ambulatory Infusor® pump. In Cancer Care Alberta (CCA), Baxter Elastomeric Infusors® are utilized. These Infusors® are non-electronic medication pumps whereby medication is delivered to the patient as the elastomeric “balloon” consistently and gently pushes solution through the IV tubing and into the catheter/port. The Infusors® are available in a variety of volumes and flow rates and flow within +/- 10% of the labelled flow rate. In addition, various environmental factors can affect the accuracy of flow rate parameters as outlined below. It is important to note that there is this expected variation in flow rate accuracy and this guideline is intended to address situations where there has been an unanticipated significant variation in the expected flow rate.

**Table 1:** Environmental factors affecting flow rate<sup>4</sup>.

<b>Temperature</b>	The Infusor® flow rate is most accurate at 33.3°C.* Flow rate will decrease ~2.3% per 1°C decrease in temperature. *LV10 Infusor® (2C1063KP) and LV1.5 (2C1087KP) Infusor® are designed to operate at optimum flow rate when Luer Lock® connector is at 31.1°C	
<b>Viscosity</b>	The Infusor® flow rate is most accurate with a diluent solution of 5% Dextrose. An Infusor® filled with 0.9% sodium chloride (NaCl) as a diluent will flow ~10% faster than labelled rate.	Note: CCA pharmacy uses 5% dextrose in water (D5W) to prepare Infusors®.
<b>Access</b>	To ensure an accurate flow rate, the access system should be 22 gauge or larger when using an Infusor®.	
<b>Fill volume</b>	Infusor® flow rate is most accurate when filled to the labelled nominal volume. Infusors® flow faster than labelled flow rate if UNDERFILLED (filled to < 81% of optimal fill volume).	Note: CCA pharmacy prepares Infusors® to nominal fill volume.
<b>Pump Height</b>	Flow rate is most accurate when the balloon reservoir and the Luer Lock® connector are at the same height. Flow rate can decrease ~ 0.5% per 2.5 cm if the balloon reservoir is below the Luer Lock® connector. Flow rate can increase ~ 0.5% per 2.5 cm if the balloon reservoir is above the Luer Lock® connector.	

Prescribing medical staff, pharmacy and nursing must follow procedures to minimize the risk of an error in dose calculation or incorrect selection of the Baxter Elastomeric Infusors® device. In the event of a fluorouracil overdose/overinfusion, appropriate and timely measures should be implemented per the recommendations outlined below.

## Guideline Question

1. What is the recommended management strategy for a potential overdose of fluorouracil infusion?

## Search Strategy

This guideline was originally developed in 2016 to ensure the safe management of a fluorouracil infusion overdose for patients in Alberta. A literature review was conducted in July, 2022 and did not result in any major updates. The guideline was originally adapted from the 2015 BC Cancer Agency (BCCA) Cancer Management Guideline: Management of 5-fluorouracil (5FU) infusion overdose at the BCCA<sup>1</sup> (Interim Guidance).

## Target Population

This guideline applies to adult patients with cancer who are being treated with fluorouracil.

## Recommendations

1. The BCCA defines a fluorouracil Infusor® overdose as administration of fluorouracil via Infusor® at  $\geq 2$  times the intended rate with completed delivery of greater than 50% of the intended total fluorouracil dose. As per manufacturer's instructions, an overdose can be determined by visual inspection<sup>4</sup>. A photo of the empty Infusor® device can be found in the [CancerCare Alberta Standard Operating Process Elastomeric Ambulatory Infusion Pumps](#).
2. Upon identification of a potential overdose, the patient will be instructed to return to a CCA facility (or the closest emergency department if after-hours) for assessment. The fluorouracil Infusor® should be discontinued and the approximate total administered dose of fluorouracil should be determined.
3. The most involved clinician(s) should be paged and informed of the potential infusion error, with details regarding the over-infusion rate, the total dose delivered and the patient's current clinical status and vitals.
4. Convene a Rapid Response Team (RRT) as outlined in the [AHS Procedure: Immediate and Ongoing Management of Clinical Adverse Events](#).
5. Contact the Alberta Poison Control Center at 1-800-332-1414 for a toxicology consult if clinically indicated.
6. The Infusor® should be weighed immediately by pharmacy or nursing staff and compared to the empty weight of the Infusor®. See appendix to calculate the amount of fluorouracil potentially infused.

**If the overdose rate is between 2-10X intended rate (with completed delivery of greater than 50% of the intended total fluorouracil dose):**

- Hospitalization at discretion of medical team.
- Consider:
  - Degree of overdose – greater vigilance may be required for overdoses between 8-10X intended rate.
  - Patient factors which may be associated with impaired clearance including advanced age, impaired baseline renal function (CrCl < 60 mL/min) and impaired hepatic function (AST > 2.5X ULN, Bilirubin > 1.5X ULN).
  - Patient's ability to return for close outpatient follow-up and monitoring.
  - Patient's access to home and social supports.
- Initiate filgrastim (G-CSF) at a dose of 5 mcg/kg sc daily 24 hours after disconnecting the pump and continuing for a minimum of 7 days or until past nadir to ANC  $\geq$  1.0.<sup>3,5</sup>
- Discontinue concomitant medications which may impair clearance of fluorouracil: cimetidine, metronidazole, and thiazide diuretics.<sup>6</sup>
- Start the patient on broad spectrum antibiotic prophylaxis.
- If managed as an outpatient:
  - Clinical assessment every 1-2 days for 7 days then as required.
  - Labs every 1-2 days for 7 days then as required: CBC, electrolytes, LFTs and creatinine monitoring.
- If on combined modality therapy – notify responsible Radiation Oncologist and hold radiation therapy, be aware if pelvic irradiation is underway that myelosuppression may be worse than what would be expected by fluorouracil alone.
- Consider contacting [PADIS](#) for additional information.
- Inform administration, medical, nursing and pharmacy leadership of the patient event.

**If the overdose rate is greater than 10X intended rate (with completed delivery of greater than 50% of the intended total fluorouracil dose):**

- Patient should be hospitalized for monitoring and supportive management including assessment of hemodynamic status and intravenous hydration.<sup>4</sup>
- Obtain a baseline ECG.
- Daily CBC, electrolytes, LFTs, creatinine.
- Discontinue concomitant medications which may impair clearance of fluorouracil: cimetidine, metronidazole, and thiazide diuretics.<sup>6</sup>
- Initiate filgrastim (G-CSF) at a dose of 5 mcg/kg sc daily 24 hours after disconnecting the pump and continuing for a minimum of 7 days or until past nadir to ANC > 1.0.<sup>3,5</sup>
- Start the patient on broad spectrum antibiotic prophylaxis.
- Initiate glutamine 18 g PO daily for prevention of fluorouracil intestinal toxicity.<sup>7,8</sup>
- Administration of uridine triacetate (Vistogard, Wellstat) is strongly advised.<sup>9</sup>

- Uridine triacetate is an oral prodrug of uridine, a specific pharmacologic antidote for fluorouracil poisoning.
- It is recommended that treatment with uridine triacetate should commence as soon as possible (8-96 hours) after a suspected severe fluorouracil overdose.<sup>6</sup>
- See Appendix B for detailed instructions for obtaining uridine triacetate.
- Dosing regimen from Wellstat Therapeutics:<sup>10</sup>
  - Adults (≥ 18 years): One sachet or orange-flavored coated granules (contains 10 g of uridine triacetate/dose) taken every six hours for a total of 20 doses. It is recommended that granules be mixed with applesauce, pudding, yogurt, or similar food to make the ingestion easier and followed by 8 ounces of water. The first dose is to be taken as soon as possible after the fluorouracil overdose has occurred but not less than 3 hours according to the manufacturer due to potential interference with fluorouracil renal clearance. If the patient vomits within 2 hours of administration of uridine triacetate the dose can and should be repeated.
  - Consider ondansetron 8 mg po 20 minutes before each dose of uridine triacetate to prevent nausea and vomiting<sup>11</sup>. It is reasonable to administer up to 32 mg of ondansetron/day in split doses in the absence of significant electrolyte abnormalities in magnesium or potassium or a history of long QT syndrome.
- Initiate fluoroquinolones in the event of diarrhea if not already initiated.
- If on combined modality therapy – notify responsible Radiation Oncologist and hold radiation therapy, be aware if pelvic irradiation is underway that myelosuppression may be worse than what would be expected by fluorouracil alone.
- Avoid medications that might interfere with absorption of the antidote (e.g., bismuth subsalicylate, sucralfate, cholestyramine) and use caution with medications that are metabolized by cytochrome P450 2C9 (e.g., phenytoin, clozapine).<sup>12</sup>
- Consider contacting [PADIS](#) for additional information.
- Consider an ACEI to reduce risk of 5FU-related cardiac dysfunction.
- Inform administration, medical, nursing and pharmacy leadership of the patient event.

*\*Please note Alberta Health Services (AHS) insite links may only be accessed on AHS computers\**

## Appendix A: Estimated Weights of Baxter Elastomeric Infusors®

The Baxter Elastomeric Infusors® weights included below are an estimate determined by an Alberta CancerControl pharmacy quality control project.<sup>11</sup>

The fluorouracil concentration varies between each patient's pump, but the total volume and flow rates are constant at 230 mL and 5 mL/hr. The weight of the pump empty is approximately 83.4 g. This is inclusive of the pump, its protective bag, label etc. to reflect the reality in a clinic setting that someone would have to weigh the pump. The weight of the pump full, with 230 mL of fluorouracil solution is approximately 316 g.

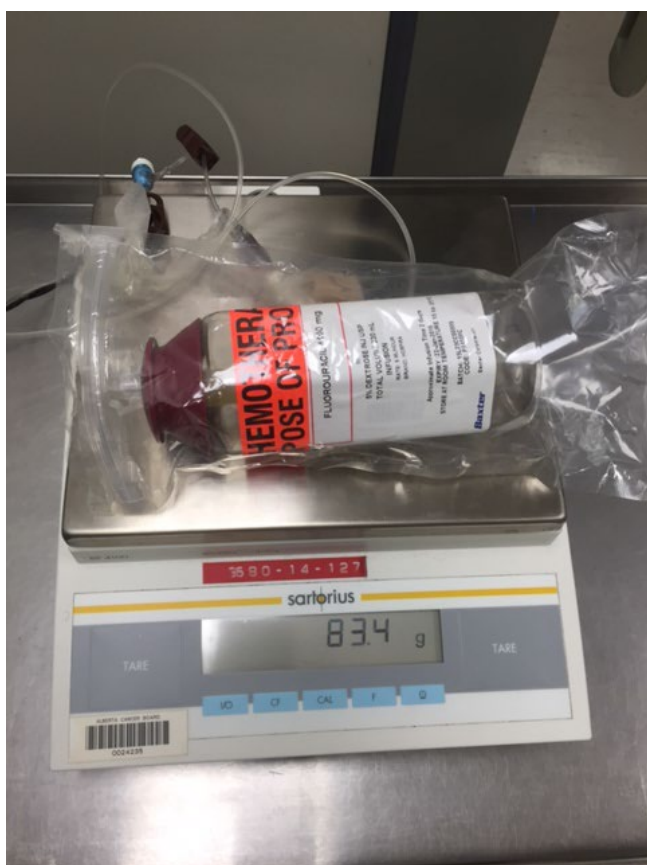
The following sample calculations can be used to estimate fluid administered and remaining (with the assumption that the specific gravity of the fluorouracil solution is 1.0 g/mL)\*:

### **Estimated amount of fluorouracil fluid administered (A) = 316 - current pump weight**

This can be used to calculate how much of the pump has infused:  $A \text{ (g=mL)} / 5 \text{ mL/hr} = \text{hours infused}$

### **Estimated amount of fluorouracil fluid left (B) = current pump weight - 83.4**

This can be used to calculate the time left to infuse:  $B \text{ (g=mL)} / 5 \text{ mL/hr} = \text{hours left to infuse}$



\* The assumption that the specific gravity of fluorouracil is 1 is based on the following observations and calculations. The average mass of the fluorouracil pumps empty measured on the pharmacy scale was 76.02 g (n=10). The average mass of the fluorouracil pumps when filled with 230 mL of the fluorouracil solution was 308.48 g (n=10). The mass of 230 mL of fluorouracil was 232.46 g; the density of the fluorouracil solution was  $232.46 \text{ g} / 230 \text{ mL}$ , which gives 1.01 g/mL. For simplicity of the calculations and allow quick estimation of the amount of fluorouracil remaining in the pump we have assumed the density of fluorouracil is 1 g/mL or a specific gravity of 1.0.

**Figure 1.** Weighing of a Baxter Elastomeric Infusor®

## Appendix B Instructions for Obtaining Uridine Triacetate<sup>13</sup>

Note that Uridine Triacetate (Vistogard) is approved for use in the United States only. Wellstat does provide uridine triacetate on a compassionate use basis, however, **it can only be shipped to the hospital in which the patient is being/will be treated.**

**Step 1** - Physician to contact Wellstat at one of the following phone numbers: Emergency hotline 443-831-5626; Wellstat Safety Phone 240-479-1078 or 240-479-1073 or 800-914-0071

Wellstat requires that the following information on the patient potentially needing treatment with uridine triacetate be provided prior to the shipment of the uridine triacetate.

- Patient's Initials
- Patient's Date of Birth or Age
- Patient's Gender, Race, Height and Weight
- Patient's Cancer Being Treated and Date of Diagnosis
- What cycle number of 5-FU or capecitabine was this? What was the intended dose of 5-FU or how much capecitabine did the patient take?
- Date and time of the 5-FU or capecitabine overdose (**Important: this is the date and time that the 5-FU infusion stopped or the date and time that the last dose of capecitabine was taken**)
- Duration of the 5-FU overdose or capecitabine overdose (start/stop times – local time)
- Planned duration of the 5-FU infusion or the capecitabine treatment.
- If the overdose was with infusional 5-FU, was a 5-FU bolus dose given? If so, how much and how long prior to the infusion was the bolus dose administered?
- If this is a case of early onset of toxicities after treatment with 5-FU infusion or capecitabine, has the patient been tested for DPD deficiency? If so, are the results available?
- If this patient is experiencing early onset of serious toxicities, please provide a list of the symptoms the patient has been experiencing and is currently experiencing.
- Does the patient have compromised renal function?

**Step 2** - Physician (with assistance from clinical pharmacist) to obtain Health Canada (HC) approval to treat by completing and submitting Special Access Program Form A.

<https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs/special-access-request-form.html>

Fax completed Form to (613) 941-3194, **and then phone** (613) 941-2108 to speak to an HC SAP agent to request an emergency verbal approval. (If after hours, leave message as per instructions, leave all details of your request with phone number for them to call back).

**Step 3** - When the information in **Step 1** has been received by Wellstat, the following documents will be sent to the hospital in which the patient will receive treatment with uridine triacetate. **The physician treating the patient and a legally responsible party at the hospital will be required to complete these documents.** As soon as the documents are returned to Wellstat, arrangements will be made to ship the uridine triacetate to the hospital where the patient is to receive treatment.

- Indemnification Agreement
- Non-Disclosure Agreement
- Physician's Agreement
- Synopsis: Clinical Operations Procedure
- Written authorization from your regulatory authorities allowing shipment of uridine triacetate into your country to the patient/hospital where the patient will be treated
- A Guarantee of Reimbursement

There is another set of documents that will be sent to the treating physician once the first set of documents has been returned to Wellstat. This second set of documents does not need to be returned immediately to Wellstat.



## References

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### Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial GI Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, urologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial GI Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed in 2016 and updated in 2022.

### Maintenance

A formal review of the guideline will be conducted in 2025. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

### Abbreviations

5FU, 5-Fluorouracil; AHS, Alberta Health Services; CCA, Cancer Care Alberta

### Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial GI Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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### Conflict of Interest Statements

**\*Dr. Patricia Tang** reports other from AMGEN, other from TAIHO, from ASTRAZENECA, grants from PFIZER, other from GENOMIC HEALTH, grants from ROCHE.

**Derek Tilley** has nothing to disclose.

\*Working group lead

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