

MANAGEMENT OF FLUOROURACIL (5-Fluorouracil, 5FU) INFUSION OVERDOSE GUIDELINE

This guideline has been created to ensure the safe management of a fluorouracil infusion overdose for patients in Alberta. It is adapted from the 2011 BC Cancer Agency (BCCA) Cancer Management Guideline: Management of 5-fluorouracil (5FU) infusion overdose at the BCCA (Interim Guidance) available at http://www.bccancer.bc.ca/books/Documents/Gastrointestinal/5FUInfusorOverdoseManagementGuideline_1Feb2011.pdf.

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.¹ Less common but potentially severe events can include cardiogenic shock, gastrointestinal bleeding and perforation.² For further information on fluorouracil, please refer to the [Cancer Parenteral Drug Information sheet on 5-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 CancerControl 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 Infusion Overdose Guideline is intended to address situations where there has been an unanticipated significant variation in the expected flow rate.

Environmental factors affecting flow rate.³

Temperature	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	
Viscosity	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®.
Access	To ensure an accurate flow rate, the access system should be 22 gauge or larger when using an Infusor®.	
Fill volume	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.
Pump Height	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.

RECOMMENDATIONS

- The BCCA defines a fluorouracil Infusor® overdose as administration of fluorouracil via Infusor® at ≥ 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.³ A photo of the empty Infusor® device can be found in the [Elastomeric Ambulatory Infusion Pumps AHS Nursing Policy and Procedure Manual](#).
- 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.
- 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.
- Convene a Rapid Response Team (RRT) as outlined in the [Alberta Cancer Board Policy regarding Clinical Management of a Critical Medication Event](#).
 - Alberta Health Services CancerControl's clinical pharmacologist should be emailed michael.sawyer@albertahealthservices.ca and/or paged immediately (780) 445-5867. *Dr. Sawyer can only be consulted for patients being treated at Alberta Health Services CancerControl sites.*
- 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 $\geq 1.0^{2,4}$
 - Discontinue concomitant medications which may impair clearance of fluorouracil: cimetidine, metronidazole, and thiazide diuretics⁵
 - 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 hydration⁴
 - Obtain a baseline ECG
 - Daily CBC, electrolytes, LFTs, creatinine
 - Discontinue concomitant medications which may impair clearance of fluorouracil: cimetidine, metronidazole, and thiazide diuretics⁵
 - 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^{2,4}
 - Start the patient on broad spectrum antibiotic prophylaxis
 - Initiate glutamine 10 g po four times daily for prevention of fluorouracil intestinal toxicity^{6,7}
 - Administration of uridine triacetate (Vistonuridine, Wellstat) is strongly advised⁸
 - Vistonuridine is an oral prodrug of uridine, a specific pharmacologic antidote for fluorouracil poisoning.
 - It is recommended that treatment with vistonuridine should commence as soon as possible (8-96 hours) after a suspected severe fluorouracil overdose.⁵
 - [Health Canada SAP approval](#) required (an AHS clinical pharmacist at the facility where the medication will be administered should be contacted to assist with this request and they may contact a CCI or TBCC pharmacist for further information)
 - Availability of vistonuridine is dependent upon supply from the US manufacturer (Wellstat) and may be considered by Wellstat on a case-by-case basis
 - Ensure the Nondisclosure Agreement Form, Indemnification Agreement Form, Physician Agreement, and Synopsis: Clinical Operations Procedure 401.002 provided by the US manufacturer (Wellstat) are reviewed and signed for submission¹
 - Dosing regimen from Wellstat Therapeutics¹
 - 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.⁹ 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)¹⁰
 - Consider contacting [PADIS](#) for additional information
 - Inform administration, medical, nursing and pharmacy leadership of the patient event

The recommendations contained in this overdose management guideline are a consensus of the Alberta Provincial GI Tumour Team, and synthesis of currently accepted approaches to management, adapted from the BC Cancer Agency Management Guideline for fluorouracil (5FU) infusion overdose. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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.¹¹

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: $B \text{ (g=mL)} / 5 \text{ mL/hr} = \text{hours left to infuse}$

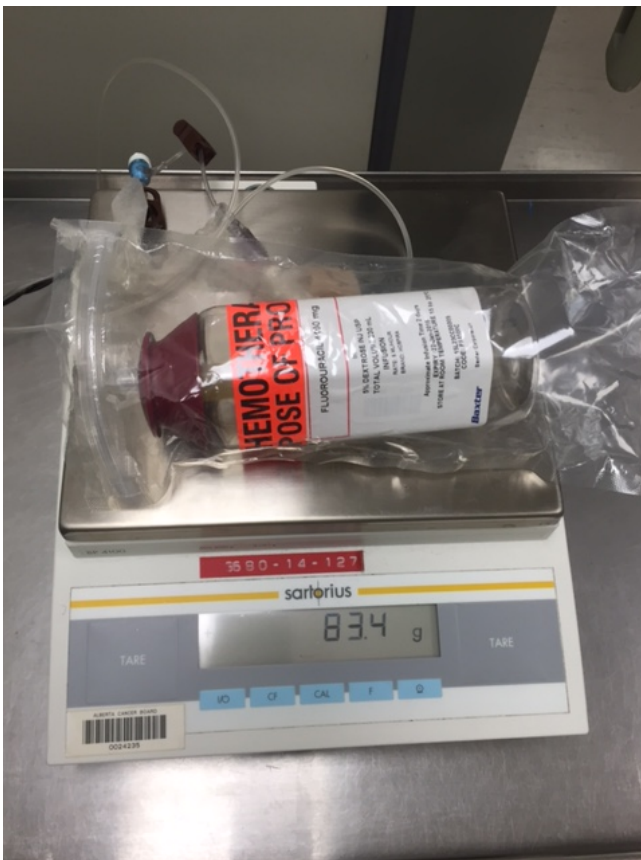


Figure 1. Weighing of a Baxter Elastomeric Infusor®

* 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 g / 230 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.

REFERENCES

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