Product Monograph

Including Patient Medication Information

[Pr] FLUOROURACIL INJECTION

Sterile Solution,
For intravenous use
250 mg/5 mL, 500 mg/10 mL, 1 g/20 mL, 5 g/100 mL
(50 mg / mL)
Manufacturer ’s Standard
Antineoplastic Agent

Generic Medical Partners Inc.

1500 Don Mills Road, Suite 711
Toronto, Ontario
M3B 3K4

Date of Authorization:
2026-02-13

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Recent Major Label Changes

3 Serious Warnings and Precautions Box	2026-02
7 Warnings and Precautions, **Endocrine and Metabolism** - Dihydropyrimidine dehydrogenase (DPD) deficiency	2026-02
7 Warnings and Precautions, **Immune** - Skin Reactions	2026-02
7 Warnings and Precautions, **Reproductive Health** - Female Contraception	2026-02
7 Warnings and Precautions, **Reproductive Health** - Male Contraception	2026-02

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1 Indications

Fluorouracil Injection (5-fluorouracil) is indicated:

- in the palliative treatment of colorectal carcinoma and carcinoma of the breast, and in the treatment of carcinoma of the stomach, pancreas, prostate, ovary, bladder and head and neck, either as a single agent or in combination with radiation therapy and/or other chemotherapeutic agents.

- as adjuvant therapy in colorectal and breast cancer.

Fluorouracil Injection is not intended to be used prophylactically.

1.1 Pediatrics

Pediatrics (≤ 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 Contraindications

- Fluorouracil (5-fluorouracil) therapy is contraindicated in pregnant women, for patients in a poor nutritional state, those with severely depressed bone marrow function, with potentially serious infections, or those with a known hypersensitivity to 5-fluorouracil.

- Fluorouracil Injection must not be taken within 4 weeks of treatment with brivudine, sorivudine or their chemically related analogues. Brivudine, sorivudine and their analogues are potent inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD), which degrades fluorouracil (see 9 Drug Interactions, 9.4 Drug-Drug Interactions).

- **Fluorouracil Injection is contraindicated in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. Testing for DPD deficiency should be considered prior to treatment, based on local availability and current guidelines (see 9 Drug Interactions, 9.7 Drug-Laboratory Test Interactions).**

3 Serious Warnings and Precautions Box

- **Severe skin reactions:** Cases of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving fluorouracil in combination therapy.

- **Severe toxicity (e.g., stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with 5-**

fluorouracil has been attributed to deficiency of DPD activity, an enzyme involved in fluorouracil degradation. Fatalities have been reported. Testing for DPD deficiency should be considered prior to treatment, based on the local availability and current guidelines (see 7 Warnings and Precautions, Endocrine and Metabolism).

4 Dosage and Administration

4.1 Dosing Considerations

Criteria for the selection of patients: In order to be considered for Fluorouracil Injection (5-fluorouracil) therapy, a prospective patient must meet the following:

- No history of high irradiation to major bone marrow-bearing areas.
- Adequate bone marrow function, i.e., a white blood cell count of 3000/mm^3 or over,
- A granulocyte count of 1500/mm^3 or over and a platelet count of 80 000/mm^3 or over.
- Adequate hepatic and renal functions.

Fluorouracil Injection (5-fluorouracil) should only be administered intravenously, and care should be taken to avoid extravasation. No dilution of the solution is required when Fluorouracil Injection is given by direct intravenous injection.

4.2 Recommended Dose and Dosage Adjustment

In most cases, dosage should be based on the patient's actual weight or actual body surface area. However, if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention, the ideal weight or ideal body surface area should be used. Following major weight loss, the dose of 5-fluorouracil should be reduced.

5-fluorouracil is a highly toxic drug with a narrow margin of safety.

Therapeutic response is unlikely to occur without some evidence of toxicity. Patients should be informed of expected toxic effects, particularly oral manifestations (see 8 Adverse Reactions).

It is recommended that each patient be carefully evaluated prior to treatment, in order to estimate as accurately as possible the optimum initial dosage of Fluorouracil Injection. Likewise, the duration of therapy must be determined by a specialist, based on the type and course of the disease.

The following dosage schedules may be used:

Recommended Dose

Initial therapy

Daily dosage generally should not exceed 800 mg. In good risk patients, a dose of 12 mg/kg (500 mg/m^2) via injection is given daily for 5 days and repeated every 28 days. In poor risk patients a dose of 6 to 10 mg/kg (250 to 400 mg/m^2) is given daily for 5 days and repeated every 28 days. When used in combination with other chemotherapeutic agents, various schedules may be used including a single dose per course, a dose on day 1 and day 8 and daily for 4 or 5 days. The dose given varies, depending on the regimen used. A sequence of 1 to 5 injections constitutes a "course of therapy".

Administration by infusion may result in slightly less toxicity. Diluted solutions (see 4 Dosage and Administration) of Fluorouracil Injection may be given each day in an intravenous drip infusion, over a period of 4 hours. The dosages should be 12 mg/kg or 480 mg/m^2 daily for most patients (maximum 800 mg/day), or 6 mg/kg or 240 mg/m^2 daily for poor-risk patients (maximum 400 mg/day). These infusions should be continued daily until gastrointestinal side effects appear, which is usually the case after 8 to 15 days.

Fluorouracil may also be administered by continuous 24 hour, intra-arterial infusion, at a dosage of 5 - 7.5 mg/kg/day.

Maintenance therapy

When toxicity has not been a problem, or after the toxic signs from the initial course of therapy have subsided, therapy should be continued using either of the following schedules:

1. Repeat dosage of the first course, beginning 28 days after the first day of the previous course of treatment.

2. Administer a maintenance dosage of 10 to 15 mg/kg/week. Use reduced dosages for poor risk patients.

The drug dosage to be used should take into account the patient's reaction to the previous course of therapy and be adjusted accordingly. Some patients have received from 9 to 45 courses of treatment during periods which ranged from 12 to 60 months.

Fluorouracil and fluorouracil / leucovorin as adjuvant therapy for colon cancer

The combination of fluorouracil and leucovorin has been compared to single agent fluorouracil in several clinical trials for the adjuvant treatment of colorectal cancer. Fluorouracil as a single agent was delivered at an approximate dose of 530 mg/m^2/week, while fluorouracil with leucovorin (200 to 500 mg/m2/day) was delivered at an approximate dose of 462 mg/m^2/week.

When used with leucovorin, fluorouracil administered at the single-agent maximum tolerated dose has occasionally produced unacceptable toxicity. Nevertheless, lower doses of fluorouracil when combined with leucovorin have shown higher response rates than fluorouracil alone.

Cyclophosphamide, methotrexate and fluorouracil (CMF) regimen for adjuvant therapy of breast carcinoma.

Adjuvant chemotherapy with a radical or modified mastectomy in early breast cancer has been shown (statistically) to protect against the development of new primary tumors. The most common chemotherapeutic regimen is cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in estrogen-receptor-negative patients, with the addition of tamoxifen in estrogen-receptor-positive patients.

A typical CMF dosage regimen and schedule is 12 courses of cyclophosphamide 100 mg/m^2 orally on days 1 to 14, methotrexate 40 mg/m^2 intravenous on days 1 and 8, and 5-flourouracil 600 mg/m^2 intravenous on days 1 and 8. Tamoxifen, 10 mg twice a day orally, is added in the case of node-positive patients.

Dosage Reduction in Combination Therapy

When Fluorouracil Injection is combined with other cytostatics of similar toxicity profile or with radiotherapy, the recommended dosage should be reduced accordingly.

Renal Impairment

Due to the impairment of bone marrow function in azotemia, secondary to kidney failure, a dose adjustment appropriate to the degree of renal failure and to the reaction of the individual patient to Fluorouracil Injection is recommended.

Hepatic Impairment

Since 5-fluorouracil is metabolized mainly in the liver, a dosage reduction should be considered when liver function is impaired.

Note: The patient's reaction to the previous course should be taken into account when determining the dosage. Some patients have received from 9 to 45 courses of treatment over periods ranging from 12 to 60 months.

Frequent blood counts (every two or three days) are essential during initial therapy. During maintenance therapy, counts before each course are sufficient.

Therapy should be properly adjusted or discontinued whenever any of the following signs of toxicity appear:

- Significant stomatitis, mucositis or esophagitis, severe diarrhea or vomiting, or gastrointestinal ulcers or bleeding occurs.
- Leukopenia (WBC count under 3000/mm^3), thrombocytopenia (platelet count under 80 000/mm^3), or granulocytopenia (under 1500/mm^3).
- Central or peripheral nervous system toxicity, including ataxia, tremor.
- Cardiac toxicity.

4.3 Reconstitution

Parenteral Products:

Dilution

No dilution of the solution is required when Fluorouracil Injection is given by direct intravenous injection.

Fluorouracil Injection (50 mg/mL) may be diluted for intravenous infusion in plastic infusion bags or bottles, to a final concentration of 2 mg/mL in 5% dextrose injection. Dilution should be made just prior to administration and the solution used within 24 hours. Unused solution should be discarded after this time, in order to avoid the risk of microbial contamination.

4.4 Administration

Directions for Dispensing from Pharmacy Bulk Vial

The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only. Dispensing from the Pharmacy Bulk Vial should be completed as soon as possible, preferably within 8 hours after initial entry.

FLUOROURACIL INJECTION (50 mg/mL) should not be mixed directly with other chemotherapeutic agents or intravenous additives.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

5 Overdose

The main symptoms of overdose are nausea, vomiting, diarrhea, stomatitis, esophagopharyngitis, gastrointestinal ulceration and bleeding, hemorrhage from any site and bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). Uridine triacetate is a specific antidote for the treatment of 5-fluorouracil overdose or the treatment of severe early-onset toxicities. It should be administered within 96 hours after end of 5-fluorouracil infusion. In the event uridine triacetate is not available, treatment is symptomatic and supportive. Patients who have been exposed to an overdose of Fluorouracil (5-fluorouracil) should be monitored hematologically with regular white cell counts, differentials and platelet counts. Should abnormalities appear, appropriate symptomatic therapy should be utilized. Suitable counter measures are withdrawal of medication or dosage reduction and, depending on the symptoms, blood transfusions, leukocyte or platelet infusions or antiinfective therapy. Nausea, vomiting and diarrhea may be controlled by appropriate therapy.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength /Composition	Non-Medicinal Ingredients
Intravenous	Sterile Solution, 50 mg/mL	Sodium hydroxide, water for injection.

FLUOROURACIL INJECTION (50 mg/mL) is a sterile solution of fluorouracil 50 mg/mL in Water for Injection, without preservative. The pH of the solution is adjusted to 8.5 – 9.3 with Sodium Hydroxide Fluorouracil Injection is available as:

250 mg/5 mL, 500 mg/10 mL, 1 g/20 mL and 5 g/100 mL sterile, unpreserved solution in pharmacy bulk vials (single packs).

The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized intravenous admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for intravenous use only.

7 Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

Fluorouracil (5-fluorouracil) should be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and well-versed in the use of potent antimetabolites.

Severe hematological effects, gastrointestinal hemorrhage and even death may result from the use of 5-fluorouracil despite meticulous selection of patients and careful adjustment of dosage, but severe toxicity is more frequent in poor risk patients.

The drug should be used with extreme caution in patients who have undergone recent major surgery; those with a history of high dose irradiation to bone marrow-bearing areas (pelvis, spine, ribs, etc.) or previous use of other myelosuppressive chemotherapeutic agents; those with a widespread involvement of bone marrow by metastatic tumors; or those with renal or liver impairment. Although severe toxicity is more likely in debilitated patients, fatalities may be encountered occasionally even in patients in relatively good condition.

Carcinogenesis and Genotoxicity

Positive mutagenic findings have been observed in the usual mutagenicity screening tests (see 16 Non-Clinical Toxicology, Genotoxicity).

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with 5-fluorouracil (see 7 Warnings and Precautions, Special Populations). Males are advised not to father a child during treatment.

Cardiovascular

5-fluorouracil can cause myocardial ischemia, angina, precordial pain, cardiac arrhythmias, ischemia and heart failure. In the case of cardiac toxicity, continued treatment with 5-fluorouracil is not recommended.

Endocrine and Metabolism

Dihydropyrimidine dehydrogenase (DPD) deficiency

5-fluorouracil should be used with great care in patients who are known or suspected to have a dihydropyrimidine dehydrogenase deficiency, as these patients are at a greater risk of experiencing symptoms of toxicity.

Severe toxicity (e.g., stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with fluorouracil has been attributed to a deficiency of dihydropyrimidine dehydrogenase (DPD) activity. Fatal outcome has been reported in some cases. Absence of this catabolic enzyme appears to result in prolonged clearance of fluorouracil. Special attention should be given to DPD status when evaluating patients experiencing fluorouracil-related toxicities. No dose has been proven safe for patients with complete absence of DPD activity.

Patients with certain heterozygous DPYD variants (e.g., DPYD*2A variant) that may cause partial DPD deficiency have been shown to have increased risk of severe toxicity when treated with 5-fluorouracil. For patients with partial DPD deficiency where the benefits of 5-fluorouracil are considered to outweigh the risks (taking into account the suitability of an alternative non-fluoropyrimidine chemotherapeutic regimen), these patients must be treated with extreme caution, initially with a substantial dose reduction and frequent subsequent monitoring and dose adjustment according to toxicity.

Testing for DPD deficiency should be considered prior to treatment, based on the local availability and current guidelines.

In patients with unrecognized DPD deficiency treated with 5-fluorouracil as well as patients who test negative for specific DPYD variations, life-threatening toxicities manifesting as acute overdose may occur. In the event of grade 2-4 acute toxicity, treatment must be discontinued immediately. Permanent discontinuation should be considered based on clinical assessment of the onset, duration and severity of the observed toxicities (see 4 Dosage and Administration).

Gastrointestinal

Diarrhea

5-fluorouracil can cause severe diarrhea or vomiting, or gastrointestinal ulcers or bleeding. Diarrhea usually responds to antidiarrheal agents (see 4 Dosage and Administration). In the case of severe gastrointestinal toxicity continued treatment with 5-fluorouracil is not recommended.

Hematologic

Because of the possibility of leukopenia, frequent blood counts (every two or three days) are essential during initial therapy. If the count falls, it is advisable to obtain differentials with each count. If the count is less than 1500/mm^3 with marked granulocytopenia (less than 1000/mm^3), it is recommended that the patient be carefully followed and considered for prophylactic antibiotics. During maintenance therapy, counts before each course are sufficient.

Hepatic/Biliary/Pancreatic

Hepatic Insufficiency

Patients with hepatic impairment should be carefully monitored with 5-fluorouracil is administered (see Monitoring and Laboratory Tests).

Immune

Skin Reactions

Cases of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving fluorouracil in combination therapy (see 8 Adverse Reactions, Skin).

Monitoring and Laboratory Tests

- Testing for DPD deficiency should be considered prior to treatment, based on the local availability and current guidelines (see 7 Warnings and Precautions, Endocrine and Metabolism).
- Patients should be carefully monitored for toxicity (see 4 Dosage and Administration).
- Patients with severe diarrhea should be monitored for symptoms of dehydration (see 7 Warnings and Precautions, Gastrointestinal).
- Patients with hepatic impairment or renal insufficiency should be carefully monitored when 5-fluorouracil is administered (see 7 Warnings and Precautions; 4 Dosage and Administration, Hepatic Impairment).
- Pregnancy testing is recommended for females of reproductive potential prior initiating 5-fluorouracil (see 7 Warnings and Precautions, 7.1 Special Populations).

Neurologic

Fluorouracil can cause neurologic toxicity including Ataxia, dysarthria, nystagmus, disorientation, headache, confusion, euphoria, acute cerebellar syndrome (which may persist following discontinuation of treatment). Extra pyramidal or cortical dysfunction (usually reversible). Isolated cases of leucoencephalopathy have also been reported. In the case of neurological toxicity, continued treatment with 5-fluorouracil is not recommended.

Renal

Renal Insufficiency

Due to the impairment of bone marrow function in azotemia, secondary to kidney failure, a dose adjustment of 5-fluorouracil is recommended (see 4 Dosage and Administration).

Reproductive Health

- **Fertility**

  Based on evidence from animal studies, 5-fluorouracil may impair fertility in females and males of reproductive potential (see 16 Non-Clinical Toxicology).

- **Female Contraception**

  Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with 5-fluorouracil and be provided with appropriate counselling if not currently using contraceptives. An effective method of contraception should be used during treatment and for 6 months after the last dose of 5-fluorouracil. If the patient becomes pregnant while receiving 5-fluorouracil, the potential hazard to the fetus must be explained. Pregnancy testing is recommended for females of reproductive potential prior initiating 5-fluorouracil (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

- **Male Contraception**

  Male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose of 5-fluorouracil.

7.1 Special Populations

7.1.1 Pregnancy

Although it is not known whether 5-fluorouracil crosses the human placenta, it has been shown to cross the rat placenta and enter into the fetal circulation of this rodent. Positive teratologic findings have been observed in animals (see 16 Non-Clinical Toxicology, Teratology). Therefore, this drug should not be used during pregnancy.

7.1.2 Breastfeeding

It is not known whether 5-fluorouracil is excreted in human milk. Because 5-fluorouracil inhibits DNA, RNA and protein synthesis, mothers should not nurse while receiving this drug.

7.1.3 Pediatrics

Pediatrics (≤ 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 Adverse Reactions

8.1 Adverse Reaction Overview

Stomatitis, mucositis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are commonly seen during therapy with Fluorouracil (5-fluorouracil). Allergic reactions including anaphylaxis, bronchospasm, urticaria and pruritus have also been reported. If anaphylactic shock occurs, the usual countermeasures should be employed. Diarrhea usually responds to antidiarrheal agents. Uncontrolled nausea and vomiting can be treated with antiemetic agents.

Leukopenia with neutropenia usually follows each course of adequate therapy with 5-fluorouracil. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first dose, although the maximal depression may occasionally be delayed for as long as 20 days. By the 30th day, the count usually returns to the normal range. Pancytopenia, agranulocytosis, anemia, hemolytic anemia and thrombocytopenia have also been reported. Due to immunosuppression, infections (sometimes serious), may develop in patients treated with 5-fluorouracil.

Alopecia and dermatitis may be seen in a substantial number of cases. Patients should be alerted to the possibility of alopecia, but since the alopecia is reported to be reversible, special measures do not seem

to be indicated. The dermatitis seen most often is a pruritic maculopapular rash appearing usually on the extremities and sometimes on the trunk. It is generally reversible and responsive to symptomatic treatment.

8.2 Clinical Trial Adverse Reactions

Cardiovascular: Myocardial ischemia, angina, precordial pain, cardiac arrhythmias, ischemia and heart failure resulting rarely in death.

Gastrointestinal: Gastrointestinal ulceration and bleeding.

Miscellaneous: Thrombophlebitis, epistaxis, nail changes (including loss of nails), chest pain, vein pigmentation. Hepatocellular damage and, in very rare cases, fatal hepatic necrosis have been observed.

Neurologic: Ataxia, dysarthria, nystagmus, disorientation, headache, confusion, euphoria, acute cerebellar syndrome (which may persist following discontinuation of treatment). Extra pyramidal or cortical dysfunction (usually reversible). Isolated cases of leucoencephalopathy have also been reported.

Ophthalmic: Visual changes; photophobia; oculomotor disturbances and lacrimation, optic neuritis. Lacrimal duct stenosis (canalicular fibrosis) associated with prolonged administration of fluorouracil has been reported as rare. This condition is reversible upon reduction or temporary cessation of 5-fluorouracil therapy, but on occasion may necessitate surgical intervention.

Skin: Dry skin; fissuring; photosensitivity as manifested by erythema or increased pigmentation of the skin; palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome), as manifested by tingling of the hands and feet followed by pain, erythema and swelling. Palmar-plantar erythrodysesthesia syndrome gradually resolves 5 to 7 days after interruption of therapy. This syndrome may be treated with the concomitant oral administration of pyridoxine at doses of 100 to 150 mg per day.

Cases of Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving fluorouracil in combination with other agents known to be associated with these disorders. A contributory role of fluorouracil in these occurrences of SJS/TEN cannot be excluded.

9 Drug Interactions

9.4 Drug-Drug Interactions

Brivudine, sorivudine or their chemically related analogues irreversibly inhibit DPD, resulting in a significant increase in fluorouracil exposure. This may lead to increased fluoropyrimidine-related toxicities with potentially fatal outcome. Therefore, either a different antiviral therapy may be used or there should be an interval of at least 4 weeks between the administration of brivudine, sorivudine, or the analogues and the start of fluorouracil treatment (see 2 Contraindications). In the case of accidental administration of nucleoside analogues that inhibit DPD activity to patients treated with fluorouracil, effective measures should be taken to reduce fluorouracil toxicity. Immediate hospitalization is recommended.

Leucovorin (folinic acid) and 5-fluorouracil are routinely used together in the treatment of colorectal cancer. There is biochemical rationale for the synergism produced by the combination of 5-fluorouracil and leucovorin. Leucovorin is metabolized to a reduced folate co-factor that is necessary for maximal inhibition of thymidylate synthetase by Fd-UMP, the active metabolite of 5-fluorouracil. Studies with tumour lines *in vitro* have confirmed this effect and several clinical studies have shown evidence that there may be some increased therapeutic benefit from providing a source of reduced folate.

Clinical trials have been reported using sequenced methotrexate/fluorouracil in head and neck, breast and colorectal cancers. Methotrexate has been shown to improve the effectiveness of 5-fluorouracil against tumor cells *in vitro* and *in vivo*. The sequence of administration is of importance. Administration of methotrexate followed by 5-fluorouracil leads to a synergistic interaction. Biochemical modulation might occur both through effects on RNA and DNA synthesis and enhancement of 5-fluorouracil uptake. The importance of the time interval between methotrexate and 5-fluorouracil exposure in the treatment of metastatic colon cancer has been demonstrated. When these two agents are separated by 24 hours as compared with 1 hour, the response rate, time to progression and survival are significantly improved. However, different tumors may respond differently to changes in the time interval between methotrexate and 5-fluorouracil.

Any form of therapy which adds to the stress of the patient, interferes with nutrition, or depresses bone marrow function, may increase the toxicity of 5-fluorouracil.

When combining 5-fluorouracil with other anticancer agents (such as methotrexate, cyclophosphamide, cisplatin, vincristine, mitomycin, adriamycin, levamisole or interferon alpha-2a) and leucovorin, drug interactions increasing both the efficacy and/or toxicity have been reported. A hemolytic-uremic syndrome has been reported to occur after long-term use of 5-fluorouracil in combination with mitomycin.

Treatment with cimetidine for several weeks before initiation of fluorouracil treatment may increase plasma fluorouracil concentrations. This effect is probably due to both inhibition of hepatic enzymes and reduction of hepatic blood flow. Caution should be taken if the patient receives fluorouracil and cimetidine concurrently; some fatal outcomes have been reported.

Metronidazole may enhance the toxicity of fluorouracil. The mechanism of interaction is presumed to be reduced clearance of fluorouracil by metronidazole. Concurrent administration should be avoided; some fatal outcomes have been reported.

Elevated INR levels and occasional episodes of bleeding have been reported during concomitant use of warfarin and fluorouracil or its analogues. In these cases, fluorouracil has usually been administered as one component of an antineoplastic combination regimen. Adequate anticoagulant response to warfarin and other coumarin-derivative therapy should be monitored regularly in patients taking fluorouracil; some fatal outcomes have been reported.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

The results of tests for bilirubin (icteric index), and for 5-hydroxyindole acetic acid in the urine, may be increased or false positive.

Testing for DPD deficiency should be considered prior to treatment, based on the local availability and current guidelines (see 7 Warnings and Precautions).

10 Clinical Pharmacology

10.1 Mechanism of Action

Fluorouracil (5-fluorouracil) is a fluorinated pyrimidine antimetabolite which is structurally similar to uracil, one of the necessary building blocks in cellular division and growth.

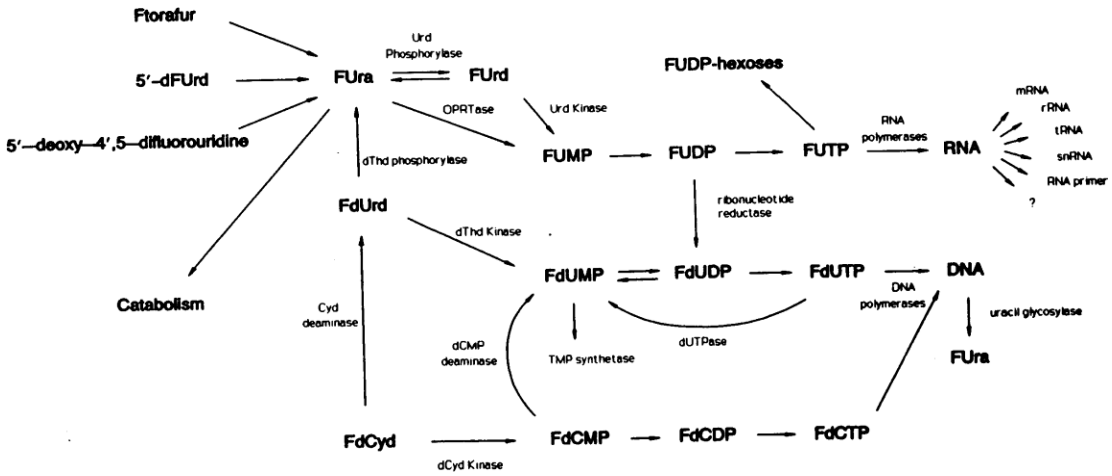


Figure 1

Its usefulness is based on uracil being utilized preferentially for nucleic acid biosynthesis in some tumors. 5-fluorouracil is metabolized to 5-fluorouridine triphosphate (F-UTP), 2-deoxyfluorouridine monophosphate (Fd-UMP), and 2-deoxyfluorouridine triphosphate (Fd-UTP) in cells to concentrations that result in both DNA-directed and RNA-directed cytotoxicities (see Figure 1). Fd-UMP is the intracellular cytotoxic form of 5-fluorouracil. It competes with the natural substrate d-UMP (deoxyuridine monophosphate) for the catalytic site on thymidylate synthetase (a key enzyme in DNA synthesis), forming a covalent complex with the enzyme that is unable to undergo the normal catalytic reaction of converting d-UMP to d-TMP. The presence of a reduced folate cofactor is required for tight binding of Fd-UMP to thymidylate synthetase. Folinic acid (leucovorin), which is metabolized to 5, 10-methylene-tetrahydropteroylglutamine (a reduced folate), is able to modulate the antineoplastic effect of 5-fluorouracil by promoting the formation and stabilization of the ternary complex formed between Fd-UMP and thymidylate synthetase. In this way, leucovorin produces a synergistic effect on 5-fluorouracil therapy.

At the same time, 5-fluorouracil interferes with the mechanism of action of RNA, resulting from the formation of «fraudulent» RNA by the incorporation of F-UTP in the ribonucleotides. Incorporation into

RNA has been associated with toxicity and has major effects on both the processing and functions of RNA.

By interference with the formation of DNA and RNA, 5-fluorouracil provokes unbalanced growth and death of cells. The effects of DNA and RNA deprivation are most marked on those cells which grow rapidly and which take up 5-fluorouracil rapidly.

While there is no evidence that 5-fluorouracil prolongs survival time generally, the usefulness of the drug has been demonstrated by the relief of pain and other symptoms in certain types of human malignancies. There have also occasionally been regression of tumors.

10.3 Pharmacokinetics

The steady-state plasma concentrations of 5-fluorouracil following bolus IV doses of 400-600 mg/m^2 (10-15 mg/kg) range from 0.1-1.0 mM. Following continuous infusion of 1100 mg/m^2/day, plasma concentrations of 0.5-2.5 mcM are observed. 5-fluorouracil readily penetrates the blood-brain barrier and CSF concentrations of about 7 mcM are reached within 30 minutes after intraveneous administration. The volume of distribution of 5-fluorouracil ranges from 0.1 to 0.4 L/kg.

The elimination half-life is 6-20 minutes and is dose-dependent. Following an IV injection, no intact drug can be detected in the plasma after three hours. For bolus doses, 5-fluorouracil plasma clearance is 0.5 to 1.4 L/min. Clearance values are 10- to 60-fold higher following IV infusion. This non-linearity likely represents saturation of a metabolic or transport process at higher drug concentrations. Plasma protein binding of 5-fluorouracil is 10%.

The metabolism of 5-fluorouracil occurs mainly in the liver and results in degradation products (e.g., carbon dioxide, urea, alpha-fluoro-beta-alanine) which are inactive. Approximately 15% of the dose is excreted intact in the urine in 6 hours and over 90% of this is excreted intact in the first hour; 60 to 80% is excreted as respiratory carbon dioxide in 8 to 12 hours.

11 Storage, Stability, and Disposal

Store unopened vials between 15 and 25°C. Protect from light and freezing

The product is available in a white glass vial. It is recommended that the vial remains in the carton until time of use. The Fluorouracil Injection vial should be inspected for damage and visible signs of leaks before use. If there are signs of breakage or leakage from the vial, do not use. Incinerate the unopened package.

Although the solution may discolor slightly to a faint yellow color during storage, the potency and safety are not adversely affected. The use of a highly colored solution is not recommended as the increased color is indicative of degradation.

If a precipitate is formed as a result of exposure to low temperatures, redissolve it by heating to 60°C with vigorous shaking, and allow to cool to body temperature prior to use.

Dispensing from the Pharmacy Bulk Vial should be completed as soon as possible, preferably within 8 hours after initial entry.

12 Special Handling Instructions

Fluorouracil (5-fluorouracil) should be administered by individuals experienced in the use of antineoplastic therapy. Fluorouracil is both an irritant and a highly toxic drug. Professional staff administering 5-fluorouracil should exercise particular care to prevent spillage and contact with the drug. Should skin contact occur, the area should be vigorously washed with soap and cold water and the material used for cleansing disposed by incineration. In the case of contact with the eyes, irrigate immediately with water and contact a physician. If inhaled or ingested, seek immediate medical attention.

1. As for all antineoplastic agents, personnel handling these agents should wear polyvinylchloride gloves, safety glasses, disposable gowns and masks and should work in vertical laminar flow hood.

2. Fluorouracil is both an irritant and a highly toxic drug. Professional staff administering antineoplastic agents should exercise particular care to percent spillage and contact with the drug. Should skin contact occur, the area should be vigorously washed with soap and water. In the case of contact with the eyes, irrigate immediately with water and contact a physician. If inhaled or ingested, seek immediate medical attention.

3. As 5-fluorouracil is frequently adsorbed by regular glass surfaces, silanized glass should be used when 5-fluorouracil is given. All materials which have come in contact with cytotoxic agents including needles, syringes, open ampoules or vials, polyvinylchloride gloves, gowns, masks and materials used for cleansing, should be segregated and incinerated at 1000°C or more. If incineration is not possible, add household bleach (sodium hypochlorite solution) or 0.1 molar sodium hydroxide solution and place the sealed container in a landfill site.

4. Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.

Part 2: Scientific Information

13 Pharmaceutical information

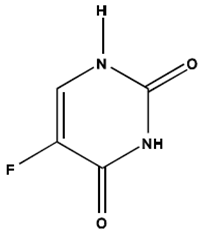
Drug Substance

Proper name: Fluorouracil (5-FU)

Chemical name: 5-fluoro-1H-pyrimidine-2,4-dione

Molecular formula and molecular mass: $C_4H_3FN_2O_2$; 130.1 g/mol

Structural formula:



Physicochemical properties:

Physical form: White to practically white, practically odorless, crystalline powder. The melting point is 280-284°C.

Solubility: Sparingly soluble in water, slightly soluble in alcohol, practically insoluble in chloroform and in ether.

14 Clinical Trials

The clinical trial data on which the original indication was authorized is not available.

15 Microbiology

Animals

5-fluorouracil has wide range of activity against the majority of solid and ascitic forms of epithelial and mesenchymal transplantable tumors of mice, rats and hamsters. Examples of these transplantable tumors include Flexner-Jobling carcinoma, Walker 256 carcinoma, Yoshida ascites tumor, Shay's chloroleukemia, Sarcoma 180, Ehrlich ascites carcinoma, L-1210 leukemia, E0771, mammary adeno-carcinoma 755 and Sarcoma A-1. 5-fluorouracil is ineffective in spontaneous mammary tumors, human epidermoid carcinoma, Harding-Passey melanoma, myeloid leukemia Db 1490, and 5-fluorouracil resistant strains of Ehrlich carcinoma and leukemia L-1210.

Tissue Cultures

5-fluorouracil inhibits the growth of Hela and H. Ep. #1 cells, both of which are epithelial-like stains derived from human cervical carcinomas, in tissue culture. The minimum active concentration inhibiting the growth of Hela cells ranges from 0.1 to 1.0 mcg/mL depending on the media used in the study. For H. Ep. #1 cells, the minimum active concentration is 1.0 mcg/mL.

Microorganisms

5-fluorouracil is a potent inhibitor of the growth of the bacteria, *Lactobacillus leichmannii*, *Lactobacillus plantarum*, *Lactobacillus casei* and *Streptococcus faecalis*, and the yeast, *Saccharomyces carlsbergensis*. The mode of action of 5-fluorouracil in these microorganisms appears to be that the drug is converted into 5-fluoro-2'-deoxyuridylic acid, a highly potent irreversible inhibitor of the enzyme thymidylate synthetase, the catalyst needed in the methylation of deoxyuridylic acid to thymidylic acid, an important reaction in the formation of DNA.

Humans

In man, the biochemical effects of 5-fluorouracil in the anabolic pathway are:

1. Inhibition of the incorporation of uracil and orotic acid in the synthesis of RNA thus inhibiting its synthesis.
2. Synthesis of an unnatural RNA by incorporation of 5-fluorouracil into the molecule.
3. Inhibition of the methylation of deoxyuridylic acid to thymidylic acid thereby inhibiting the synthesis of DNA.

5-fluorouracil is converted into fluorouridine and further into the mono-, di-, and triphosphates of fluorouridine. 5-fluorouridine monophosphate is then reduced to 5-fluoro-2'-deoxyuridine monophosphate, the apparent lethal nucleotide, which inhibits the enzyme thymidylate synthetase required in the DNA synthesis. The inhibition of DNA synthesis is considered to be chiefly responsible for the antineoplastic activity of 5-fluorouracil in man, since concentrations which inhibit DNA still permit RNA synthesis.

The catabolic pathway of 5-fluorouracil is analogous to that of uracil, forming the following degradative products: dihydrofluorouracil, alpha-fluoro-beta-ureidopropionic acid, alpha-fluoro-beta-

guanidopropionic acid, alpha-fluoro-beta-alanine, urea, and CO_2.

16 Non-Clinical Toxicology

General Toxicology

Short-Term Toxicity

LD_{50} values of 5-fluorouracil in difference species via different routes of administration are as follows:

	LD_{50} (mg/kg ± S.E.)			
Species	IV	SC	IP	PO
Mice	340 ± 17	> 250	> 500	266 ± 25
Rats	165 ± 26	--	230	303 ± 51
Rabbits	27 ± 5.1	--	--	24 ± 1.9
Dogs	31.5 ± 3.8	--	--	29 ± 3.1

The toxicity of 5-fluorouracil shows pronounced species differences. Dogs, cats and rabbits display acute intoxication resembling fluoroacetate poisoning. Convulsions are observed in cats and dogs while cardiac failure appears in rabbits. Mice, rats and monkeys tolerate 5-fluorouracil better than dogs, cats and rabbits.

Long-Term Toxicity

Excessive dosage of 5-fluorouracil in mice, rats and monkeys leads to chronic intoxication characterized by depression of cells of the bone marrow and damage to cells of the gastrointestinal mucosa. The bone marrow damage caused by overdosage is reversible upon discontinuation of 5-fluorouracil.

The approximate doses which are tolerated for varying periods of time in different species are shown in the following table:

Species	Dose (mg/kg/day)	No. of Days	Route of Administration
Mice	25	14	SC
Rats	6-12	14	SC
Rabbits	2.5	30	SC
Dogs	3-12[a]	65[b]	SC

a) One of the three monkeys receiving 12 mg/kg/day demonstrated severe toxicity and had to be sacrificed after 6 weeks of treatment.
b) Five days/week dosing for 13 consecutive weeks.

Carcinogenicity

Animal studies have demonstrated an increased incidence of some tumors in mice, but not in rats, after long-term treatment with 5-fluorouracil. Fifty male and fifty female BALB/C mice were administered 5-fluorouracil IP at a dose of 30 mg/kg body weight once a week to test the carcinogenicity of 5-fluorouracil. A significant increase in lung tumors in both sexes and tumors of the lymphoreticular system in female mice was observed.

No evidence of carcinogenicity was reported in four groups of Fischer rats administered 5-fluorouracil

by gastric intubation 5 times per week for 52 weeks, at a dose of 3.0, 1.0, 0.01 and 0.3 mg/animal per day followed by a 6 month observation period. In another study, male BR46 rats were administered weekly with IV injections of 33 mg/kg body weight for 52 weeks, followed by observations for the remainder of their lifetimes with no evidence of carcinogenesis.

Genotoxicity

Oncogenic transformation of fibroblasts from mouse embryo has been induced *in vitro* by 5-fluorouracil, but the relationship between oncogenicity and mutagenicity is not clear. 5-fluorouracil is mutagenic to several strains of *Salmonella typhimurium*, including TA 1535, TA 1537 and TA 1538, and to *Saccharomyces cerevisiae*, although no evidence of mutagenicity was found with *Salmonella typhimurium* strains TA 92, TA 98 and TA 100. A positive effect was observed in the micronucleus test on bone marrow sells of the mouse. 5-fluorouracil, at very high concentrations, produced chromosomal breaks in hamster fibroblasts *in vitro*.

Reproductive and Developmental Toxicology

5-fluorouracil has not been adequately studied in animals to permit an evaluation of its effects on fertility and general reproductive performance. However, doses of 125 or 250 mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosomal organization of spermatogonia in rats. Spermatogonial differentiation was also inhibited by 5-fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, 5-fluorouracil did not produce any abnormalities at oral doses of up to 80 mg/kg/day. In female rats, 5-fluorouracil, administered intraperitoneally at weekly doses of 25 or 50 mg/kg for three weeks during the pre-ovulatory phase of oogenesis, significantly reduced the incidence of fertile matings, delayed the development of pre- and post-implantation embryos, increased the incidence of pre-implantation lethality and induced chromosomal anomalies in these embryos. In the limited study in rabbits, a single 25 mg/kg dose of 5-fluorouracil or 5 daily doses of 5 mg/kg had no effect on ovulation, appeared not to affect implantation and had only a limited effect in producing zygote destruction. Agents such as 5-fluorouracil, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on gametogenesis.

Teratology

5-fluorouracil is teratogenic in laboratory animals. 5-fluorouracil exhibited maximum teratogenicity when given to mice as single intraperitoneal injections of 10 to 40 mg/kg on day 10 or 12 of gestation. Similarly, intraperitoneal doses of 12 to 37 mg/kg given to rats between days 9 and 12 of gestation and intramuscular doses of 3 to 9 mg given to hamsters between days 8 and 11 of gestation were teratogenic. Malformations included cleft palates, skeletal defects and deformed appendages, paws and tails. The dosages which were teratogenic in animals are 1 to 3 times the maximum recommended human therapeutic dose. In monkeys, divided doses of 40 mg/kg given between days 20 and 24 of gestation were not teratogenic.

5-fluorouracil has not been studied in animals for its effects on peri- and post-natal development. However, 5-fluorouracil has been shown to cross the placenta and enter into fetal circulation in the rat. Administration of 5-fluorouracil has resulted in increased resorptions and embryolethality in rats. In monkeys, maternal doses higher than 40 mg/kg resulted in abortion of all embryos exposed to 5-fluorouracil. Compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and post-natal development.

17 Supporting Product Monograph

1. Fluorouracil Injection USP, solution, 50 mg/mL, submission control 227813, Product Monograph, Pfizer Canada ULC. August 7, 2019

2. Fluorouracil Injection, solution, 50 mg/mL, submission control 290778, Product Monograph, Sandoz Canada Inc. May 08, 2025

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrFLUOROURACIL INJECTION

This Patient Medication Information is written for the person who will be taking **Fluorouracil Injection**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **Fluorouracil Injection**, talk to a healthcare professional.

Serious warnings and precautions box

Serious side effects of Fluorouracil Injection include:

- **Severe skin reactions:** this includes Stevens-Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN]. Some cases have been fatal.
- **Severe toxicity, including death, in patients who do not have an enzyme called dihydropyrimidine dehydrogenase (DPD).** If you lack this enzyme, you should not take Fluorouracil Injection. Your healthcare professional might check to see if you have this enzyme before you can take Fluorouracil Injection.

See the **Serious side effects and what to do about them** table, below, for more information.

What Fluorouracil Injection is used for:

- Fluorouracil Injection is used in adults for the palliative treatment of the following cancers: colon and rectum, breast, stomach, pancreas, prostate, ovary, bladder, head and neck.
  - It can be used alone or together with other treatments, such as radiation or other cancer medicines.
  - Palliative treatment helps relieve your symptoms but will not cure your disease.
- Fluorouracil Injection is used in adults after other treatments to help prevent colorectal and breast cancer from coming back.

How Fluorouracil Injection works:
Fluorouracil Injection is an antineoplastic agent that contains the medicinal ingredient fluorouracil (5-fluorouracil). These medications interfere with the growth of cells that rapidly divide in the body, including cancer cells. It prevents the growth of cancer cells and kills them.

The ingredients in Fluorouracil Injection are:
Medicinal ingredient: fluorouracil (5-fluorouracil)

Non-medicinal ingredients: sodium hydroxide, water for injection

Fluorouracil Injection comes in the following dosage forms:
Solution; 250 mg/5 mL, 500 mg/10 mL, 1 g/20 mL and 5 g/100 mL (50 mg / mL)

Do not use Fluorouracil Injection if you:

- are pregnant
- are in a poor nutritional state
- have severely suppressed bone marrow function
- have a serious infection
- are allergic to Fluorouracil Injection, fluorouracil (5-fluorouracil) or any of the non-medicinal ingredients in Fluorouracil Injection
- are being treated now, or have been treated in the last 4 weeks, with brivudine, sorivudine or a similar medicine, used to treat the viral infection herpes zoster (chickenpox or shingles)
- have been told that you do not have an enzyme called dihydropyrimidine dehydrogenase (DPD)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Fluorouracil Injection. Talk about any health conditions or problems you may have, including if you:

- have recently had a major surgery
- have had high dose radiation treatment to areas that contain bone marrow, such as your pelvis, spine, ribs, etc.
- have been treated with other medicines that suppress your bone marrow
- have tumours in your bone marrow that have spread from other locations in your body (metastasized)
- have kidney or liver problems
- plan to become pregnant
- are breastfeeding or planning to breastfeed

Other warnings you should know about:

- **Fertility:** Fluorouracil Injection can impair fertility in both male and female patients.

- **Female patients:**
    - You should not become pregnant while you are taking Fluorouracil Injection. This is because it can harm your unborn child.
    - Before you start taking Fluorouracil Injection it is recommended that you take a pregnancy test to make sure you are not pregnant.
    - You must use effective birth control while you are taking Fluorouracil Injection and for six months after you stop taking it. Talk to your healthcare professional about effective methods of birth control.
    - You should not breastfeed while you are taking Fluorouracil Injection. It is not known if it passes into breastmilk. Talk to your healthcare professional about ways to feed your baby during treatment.

- **Male patients:**
    - You should not father a child while you are taking Fluorouracil Injection.
    - If your female partner is of childbearing age, you must use effective birth control while you are taking Fluorouracil Injection and for 3 months after you stop taking it. Talk to your healthcare professional about effective methods of birth control for you and your

partner.

- **Blood tests and monitoring:**
    - Fluorouracil Injection can affect your blood cell counts, specifically your level of white blood cells. It can also cause toxicity and related side effects. Because of this , your healthcare professional will do frequent blood tests, especially when you first start taking Fluorouracil Injection, and monitor you for other side effects. They might change, reduce or stop your dose for a period of time based on your blood tests results or if other side effects appear.
    - Fluorouracil Injection can affect the results of certain urine tests. If you are going to have urine tests, tell the healthcare professional doing the test that you are taking Fluorouracil Injection.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Fluorouracil Injection:

- medicines used to treat certain viral infections like chickenpox or shingles, such as brivudine, sorivudine
- leucovorin (folinic acid), a medicine used to prevent the harmful effects of cancer chemotherapy medication
- other medicines used to treat cancer, such as methotrexate, cyclophosphamide, cisplatin, vincristine, mitomycin, adriamycin, levamisole, interferon alpha 2a
- cimetidine, used to treat heartburn and acid indigestion
- metronidazole, an antibiotic and antiprotozoal medicine used to treat infections
- blood thinner medicine, such as warfarin and other coumarin medicines

How to take Fluorouracil Injection:

- Fluorouracil Injection will be given to you in a healthcare setting.
- Fluorouracil Injection will be given to you directly into a vein (intravenously) by a healthcare professional experienced in the use of cancer medicines.

Usual dose:

Your healthcare professional will decide on the dose and length of treatment that is right for you based on your weight or body surface area and the condition being treated.

Overdose:

The main symptoms of overdose are:

- nausea
- vomiting
- diarrhea
- inflammation of the mouth, tongue and throat (stomatitis)
- inflammation of the esophagus
- ulcers and bleeding from the GI tract (vomiting blood or blood in the stool)
- unusual bleeding from anywhere in the body (hemorrhage)
- bone marrow suppression (very low levels of white and red blood cells and platelets).

If you think you, or a person you are caring for, have been given too much Fluorouracil Injection,

contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:
Talk to your healthcare professional if you have missed a dose.

Possible side effects from using Fluorouracil Injection:
These are not all the possible side effects you may have when taking Fluorouracil Injection. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- loss of appetite
- hair loss
- skin rash, irritation
- dry skin
- eye irritation, vision problems
- nail changes, including nail loss
- headache

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very common			
Diarrhea		√	
Nausea		√	
Vomiting		√	
Leukopenia / neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains, flu-like symptoms		√	
Common			
Stomatitis (inflammation of the mouth, throat and tongue): sores, ulcers, redness, pain or swelling of the mouth including inside, the tongue or the throat, problems eating		√	
Allergic reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			√
Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
(TEN) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches, swollen glands			
Rare			
Bone marrow suppression (a large decrease in the production of red blood cells, white blood cells and platelets by the bone marrow): bleeding, bruising, nose bleeds, chills, fatigue, fever, infections, weakness, shortness of breath or other signs of infection			v
Infection: cough, fever, chills, pain during urination, sore throat		√	
Heart problems: chest pain, abnormal heart rate, fainting, heart skipping a beat, shortness of breath, swelling of ankles or legs, weakness		√	
Gastrointestinal bleeding: stomach pain, vomiting blood, blood in the stool, black/tar coloured stool		√	
Liver problems: abdominal pain, dark urine, fatigue, light-coloured stool, loss of appetite, nausea, vomiting, yellowing of the skin or eyes (jaundice)		√	
Nervous system toxicity: lack of coordination or balance, tremor, trouble speaking, disorientation, headache, confusion, weakness, rapid, uncontrolled eye movements, loss of vision, personality or mood changes			√
Hand-foot syndrome: tingling, numbness, pain, swelling, redness or blisters of the palms of the hands or soles of the feet		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Fluorouracil Injection will be stored by your healthcare professional.

Keep out of reach and sight of children.

If you want more information about Fluorouracil Injection:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication information by visiting the Health Canada Drug Product Database website https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.gmprx.com; or by calling 416-444-4467.

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