**THERAPEUTIC CLASSIFICATION**

Antineoplastic

**CAUTION:** FLUOROURACIL (5-FLUOROURACIL) IS A POTENT DRUG AND SHOULD BE PRESCRIBED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE PERFORMED REGULARLY. DISCONTINUE THE DRUG IF THERE IS SIGNIFICANT LEUKOPENIA (UNDER 3000/mm³) OR GRANULOCYTOPENIA (UNDER 1500/mm³).

**INDICATIONS AND CLINICAL USE**

Fluorouracil Injection USP (5-fluorouracil) is indicated in the palliative management of carcinoma of the breast, colon, rectum, stomach and pancreas. In clinical practice, 5-fluorouracil is often combined with other cytotoxic agents such as methotrexate, cyclophosphamide, cisplatin, vincristine, mitomycin, adriamycin, levamisole and interferon alpha-2a; or drugs which may enhance its effect on killing tumor cells such as calcium leucovorin.

Various combinations of 5-fluorouracil/interferon and 5-fluorouracil/leucovorin/interferon are also used in clinical practice.

Fluorouracil Injection USP does not replace surgery or other recognized forms of therapy and should be used only when these measures are not possible or have been tried and have failed.

**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.

**WARNINGS**
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.

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.

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.

Usage in 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 TOXICOLOGY, Teratology in the product monograph). Therefore, this drug should not be used during pregnancy.

Nursing Mothers: 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.

Mutagenesis: Positive mutagenic findings have been observed in the usual mutagenicity screening tests (see TOXICOLOGY, Mutagenicity in the product monograph).

Drug Interactions - Combined Therapy
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.

PRECAUTIONS

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. (see PHARMACEUTICAL INFORMATION, Special Instructions).

5-fluorouracil is a highly toxic drug with a narrow margin of safety. Therefore, patients should be carefully supervised. Therapy should be properly adjusted or discontinued if:

- Significant stomatitis, mucositis or esophagitis, severe diarrhea or vomiting, or gastrointestinal ulcers or bleeding occurs.
- Leukopenia (WBC count under 3000/mm³), thrombocytopenia (platelet count under 80 000/mm³), or granulocytopenia (under 1500/mm³).
- Central or peripheral nervous system toxicity, including ataxia, tremor.
- Cardiac toxicity.

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

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/mm³ with marked granulocytopenia (less than 1000/mm³), it is recommended that the patient be carefully followed and considered for prophylactic antibiotics. During maintenance therapy, counts before each course are sufficient.

In the case of severe gastrointestinal, cardiac or neurological toxicity, continued treatment with 5-fluorouracil is not recommended.
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.

**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.

**ADVERSE REACTIONS**

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.

**Other Adverse Reactions**

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

**Gastrointestinal:** Gastrointestinal ulceration and bleeding.

**Central nervous system:** 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.

**Dermatologic:** 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.

**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.

**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.

### REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    - Health Canada
    - Postal Locator 0701E
    - Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

### SYMPTOMS AND TREATMENT OF 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). No specific antidotal therapy exists. 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 management of a suspected drug overdose, contact your regional Poison Control Centre.
DOSAGE AND ADMINISTRATION

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

1. No history of high irradiation to major bone marrow-bearing areas.
   Adequate bone marrow function, i.e., a white blood cell count of 3000/mm³ or over, a granulocyte count of 1500/mm³ or over and a platelet count of 80 000/mm³ or over.

2. Adequate hepatic and renal functions.

Fluorouracil Injection USP (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 USP is given by direct intravenous injection.

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.

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 USP. Likewise, the duration of therapy must be determined by a specialist, based on the type and course of the disease.

Dosage: The following dosage schedules may be used.

General Recommendations

**IV Injection**

1. 800 mg/m² (19 mg/kg) single dose.
2. 480 mg/m² (12 mg/kg) per day on days 1, 2, 3, 4 followed by 240 mg/m² (6 mg/kg) per day on days 6, 8, 10 and 12. Repeat course every 30 days.
3. 300-450 mg/m² (7-11 mg/kg) per day for 5 days. Repeat every 4 weeks.
4. 400-480 mg/m² (10-12 mg/kg) or 500-600 mg/m² (12-15 mg/kg) per week.

**IV Infusion**

Administration by infusion may result in slightly less toxicity. Fluorouracil Injection USP may be diluted with 300 to 500 mL of 5% dextrose solution.

1. 480 mg/m² (12 mg/kg) over a period of 4 hours daily until signs of toxicity are observed, usually within 8 to 15 days.
2. 1000-2000 mg/m² (24-49 mg/kg) over a period of 24 hours daily for 5 days. Repeat course every 4 weeks.

**Combination therapy with folinic acid**
IV injection 370-400 mg/m² (9-10 mg/kg) for 5 days plus folinic acid 200-500 mg/m² (5-12 mg/kg) for 5 days. Repeat course every 4 weeks. The patient must be monitored for toxic signs. Drug therapy should be appropriately adjusted or discontinued should toxic signs such as gastrointestinal bleeding become manifested.

Recommandations for Poor Risk Patients
For poor risk patients, the following dosage schedules may be used:

**IV Injection**
240 mg/m² (6 mg/kg) per day on days 1, 2, 3 followed by 120 mg/m² (3 mg/kg) per day on days 5, 7, 9. Repeat course every 30 days.

**IV Infusion**
240 mg/m² (6 mg/kg) over a period of 4 hours daily until signs of toxicity are observed, usually within 8 to 15 days.

**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 USP is recommended.

**Liver 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/mm³), thrombocytopenia (platelet count under 80 000/mm³), or granulocytopenia (under 1500/mm³).
- Central or peripheral nervous system toxicity, including ataxia, tremor.
- Cardiac toxicity.

**Dosage Reduction in Combination Therapy:**
When Fluorouracil Injection USP is combined with other cytostatics of similar toxicity profile or with radiotherapy, the recommended dosage should be reduced accordingly.

**COMPOSITION**
Fluorouracil Injection USP contains 50 mg of fluorouracil Ph.Eur. per mL of water for injection; sodium hydroxide is added to solubilize the compound and to adjust the pH to approximately 9.2.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15 and 25°C. Do not refrigerate or freeze.

Although Fluorouracil Injection USP (5-fluorouracil) solution may discolour slightly during storage, the potency, and safety are not adversely affected, and are maintained until the expiry date.

If a precipitate occurs during storage, resolubilize by heating to 60°C with vigorous shaking; allow to cool to body temperature before using.

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

Fluorouracil Injection USP may be diluted with 300 to 500 mL of 5% dextrose and administered by infusion over a period of either 4 or 24 hours (see Dosage and Administration). Infusions prepared with 5% dextrose solution should be used within 24 hours.

Special Instructions:
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 prevent 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.
AVAILABILITY

Fluorouracil Injection USP is available in:

10 mL single-dose vials containing 500 mg fluorouracil, in packs of 5 vials.

100 mL Pharmacy bulk vial containing 5 000 mg fluorouracil, in packs of 1 vial.

LATEX-FREE stoppers: stoppers contain no dry natural rubber

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