PRODUCT MONOGRAPH

[Pr]FLUOROURACIL INJECTION USP

50 mg/mL

(5 g/100 mL)

Antineoplastic Agent

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

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Control #227813

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CAUTION

FLUOROURACIL IS A POTENT DRUG AND SHOULD BE ADMINISTERED BY, OR UNDER SUPERVISION OF A PHYSICIAN, WHO IS EXPERIENCED IN CANCER CHEMOTHERAPY.

ACTIONS AND CLINICAL PHARMACOLOGY

There appears to be two mechanisms of action of fluorouracil which result in cytotoxic effects. One is the competitive inhibition of thymidylate synthetase, the enzyme catalyzing the methylation of deoxyuridylic acid to thymidylic acid. The consequent thymidine deficiency results in inhibition of deoxyribonucleic acid (DNA) synthesis, thus inducing cell death. A second mechanism of action is evidenced by the moderate inhibition of ribonucleic acid (RNA) and incorporation of fluorouracil into RNA. The predominant mechanism of antitumour action appears to be dependent, at least in part, on individual tumour intracellular metabolism.

The effects of DNA and RNA deprivation are most significant on those cells which are most rapidly proliferating.

Following intravenous injection, fluorouracil is cleared rapidly from the plasma (half-life about 10 to 20 minutes), and distributed throughout body tissues including the cerebrospinal fluid and malignant effusions, exhibiting a volume of distribution equivalent to the total body water. Plasma concentrations fall below measurable levels within 3 hours. Oral administration of fluorouracil has shown marked variability in its bioavailability, from 28% to 100%. Constant intravenous infusion for 96 hours showed constant plasma drug levels and significantly less drug (50- to 1000-fold) in the bone marrow.

Fluorouracil is converted to active nucleotide metabolites, 5-fluorouridine monophosphate and 5-fluorodeoxyuridylate within the target cell itself. Approximately 20% of an intravenous dose is excreted intact in the urine within 6 hours. The remainder is catabolized primarily in the liver where enzymatic cleavage yields α-fluoro-β-alanine, respiratory carbon dioxide, urea and ammonia. The non-linearity of fluorouracil pharmacokinetics are related to saturation of its degradation.

INDICATIONS AND CLINICAL USE

1. Fluorouracil Injection USP 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.

Listed below are tumour types and drugs used concurrently with fluorouracil:

Carcinoma of the breast
Fluorouracil with cyclophosphamide and doxorubicin; fluorouracil with cyclophosphamide and epirubicin; fluorouracil with cyclophosphamide and doxorubicin, vincristine and prednisone; cyclophosphamide, methotrexate and fluorouracil (CMF) for advanced disease as well as in the adjuvant setting of breast cancer (see below).

Carcinoma of the stomach
Fluorouracil with doxorubicin and mitomycin-C.

Carcinoma of the pancreas
Fluorouracil with doxorubicin and mitomycin-C; fluorouracil with mitomycin-C and streptozotocin.

Cancer of the urinary bladder
Fluorouracil alone; fluorouracil with doxorubicin; fluorouracil with doxorubicin and cisplatin; fluorouracil with doxorubicin and cyclophosphamide; fluorouracil with methotrexate, cyclophosphamide and vincristine.

Cancer of the prostate
Fluorouracil alone; fluorouracil with doxorubicin and cyclophosphamide.

Cancer of the head and neck
Fluorouracil with cisplatin; fluorouracil with carboplatin.

Cancer of the ovary
Fluorouracil with hexamethylmelamine, cyclophosphamide and doxorubicin.

No studies performed to date have shown malignant melanoma, kidney carcinoma, the leukemias and lymphomas, soft tissue and bone sarcomas, bronchogenic carcinoma, brain tumours and metastases to the central nervous system to be significantly responsive to fluorouracil therapy.

2. Fluorouracil is also indicated as adjuvant therapy in colorectal and breast cancer.

Colorectal cancer
Comparisons between patients receiving postoperative adjuvant chemotherapy and those treated by curative surgical resection alone have shown improved response rates and an overall improvement in disease-free survival in favour of the adjuvant chemotherapy groups.

Effective treatments have included fluorouracil in combination with other chemotherapeutic agents (semustine and vincristine for example) and fluorouracil with leucovorin modulation (the Machover regime for example), in patients with Duke's B and C colon cancer.

Breast cancer
Several studies of adjuvant chemotherapy have demonstrated a moderate reduction in the risk of recurrence in patients with primary operable breast cancer.

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 regime comprising fluorouracil, doxorubicin and cyclophosphamide (FAC) as adjuvant chemotherapy has also been found to be effective, although with risk of doxorubicin cardiotoxicity.

Fluorouracil Injection USP is not intended to be used prophylactically.

CONTRAINDICATIONS

- Fluorouracil Injection USP is contraindicated in patients who are debilitated or who have poor nutritional state, depressed bone marrow function following radiotherapy or therapy with other antineoplastic agents, or potentially serious infections, or with known hypersensitivity to the drug.

- Fluorouracil Injection USP 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 **PRECAUTIONS, Drug Interactions**).

- **Fluorouracil Injection USP 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 WARNINGS and PRECAUTIONS, Laboratory Tests).**

WARNINGS

It is recommended that fluorouracil be given only by, or under supervision of, a physician who is well acquainted with the use of potent antimetabolites.

Fluorouracil should be used with extreme caution in poor risk patients who have recently undergone surgery, have a history of high dose irradiation of bone marrow-bearing areas (pelvis, spine, ribs, etc.) or prior use of another chemotherapeutic agent causing myelosuppression, have a widespread involvement of bone marrow by metastatic tumors, or who have impaired hepatic or renal function. Clinical consequences of severe myelosuppression include infections. Viral, bacterial, fungal and/or parasitic infections, either localized or systemic, may be associated with

the use of fluorouracil alone or in combination with other immunosuppressive agents. These infections may be mild, but can be severe and at times fatal.

Fluorouracil treatment may potentiate necrosis caused by radiation.

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 taking phenytoin concomitantly with fluorouracil should undergo regular testing because of the possibility of an elevated plasma level of phenytoin (See **PRECAUTIONS, Drug interactions**).

Severe toxicity and fatalities are more likely in poor risk patients, but have occasionally occurred in patients who are in relatively good condition. Any form of therapy which adds to the stress of the patient, interferes with nutritional uptake or depresses the bone marrow function, will increase the toxicity of fluorouracil.

Some patients may experience photosensitivity reactions following administration of fluorouracil, it is recommended that patients are warned to avoid prolonged exposure to sunlight.

Cases of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving fluorouracil in combination therapy (see ADVERSE REACTIONS, Epidermal and Dermal Conditions).

Pregnancy and reproductive effects
Since fluorouracil is known to be teratogenic in animals, the drug should not be used during pregnancy, particularly in the first trimester, unless the potential benefits to the patient outweigh the hazards.

Because the risk of mutagenesis has not been evaluated, such possible effects on males and females must be considered.

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

Immunosuppressant effects/Increased susceptibility to infections
Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents including fluorouracil, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving fluorouracil. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Cardiac
Cardiac shock, cardiac failure, cardiomyopathy, myocarditis, angina, ECG abnormalities, myocardial infarction and pericarditis have been reported after administration of fluorouracil. Attention should therefore be paid to patients who experience chest pain during treatment, and patients with a history of heart disease.

PRECAUTIONS

General
Fluorouracil is a cytotoxic drug with a narrow margin of safety. Patients should be advised that therapeutic response is unlikely to occur without some evidence of toxicity.

Leukocyte counts with differential and platelet counts are recommended before each dose, and hematologic status monitored during therapy.

Prompt cessation of fluorouracil therapy should be considered if any of the following signs appear:

- Stomatitis or esophagopharyngitis (at the first visible sign of small ulceration at the inner margin of the lips)
- Intractable vomiting
- Diarrhea (watery stools or frequent bowel movements)
- Gastrointestinal ulceration or bleeding
- Hemorrhage from any site
- Leukopenia (WBC < 3,500/mm^3) or rapidly dropping WBC count
- Granulocytopenia (under 1,500 mm^3)
- Thrombocytopenia (platelets < 100,000/mm^3)

Fluorouracil should be resumed only when the patient has recovered from the above signs.

Fluorouracil should be used with caution in patients with impaired liver function and in patients with jaundice.

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 **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.

Various purines, pyrimidines and antimetabolites have shown biochemical modulation of fluorouracil in *in vitro* test systems. Purines include inosine, guanosine, guanosine-5'-phosphate and deoxyinosine. Pyrimidines include thymidine, uridine and cytidine. Antimetabolites include

methotrexate, tamoxifen, interferon, PALA, allopurinol, hydroxyurea, dipyridamol and leucovorin. Synergistic cytotoxic interactions such as those involving fluorouracil with leucovorin have shown beneficial therapeutic effects particularly in colon cancer. However, the drug combination may result in increased clinical toxicity of the fluorouracil component.

Fluorouracil causes a change in the spectrophotometric spectrum of cytarabine, possibly reducing its effectiveness. Fluorouracil mixed with methotrexate alters the spectra of both agents. Fluorouracil is physically incompatible with doxorubicin, epirubicin and with diazepam. A precipitate forms when fluorouracil is mixed with these drugs. It is recommended that complete intravenous line flushing takes place between injections of fluorouracil and cytarabine, methotrexate, doxorubicin, epirubicin or diazepam.

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.

The level of phenytoin should be regularly monitored in patients taking fluorouracil and the phenytoin dosage may need to be reduced. Toxicity associated with elevated phenytoin plasma concentrations have been reported during concomitant use of phenytoin with fluorouracil or its analogues. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by fluorouracil.

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.

Laboratory tests

Increases in serum-total-thyroxine (TT4) and serum-total-triiodothyronine (TT3) levels in euthyroid patients with advanced mammary carcinoma treated with fluorouracil used in a single drug schedule have been reported. The levels returned to pre-treatment levels within four weeks of the end of treatment.

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

ADVERSE REACTIONS

The major toxic effects of fluorouracil occur on the normal, rapidly proliferating tissues, especially those of the bone marrow and lining of the gastrointestinal tract. Stomatitis and

esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia and emesis are common (see below).

Epidermal and Dermal Conditions
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.

Infections and Infestations
Infection, Sepsis, Septic shock, Neutropenic sepsis, Pneumonia, Superinfection, Urinary tract infection, Device related infection, Cellulitis. Some fatal outcomes have been reported in case of sepsis and septic shock.

Hematological effects
Myelosuppression almost uniformly accompanies a course of adequate therapy with fluorouracil. Low WBC counts are usually first observed between the ninth and fourteenth day after the first course of treatment with the nadir occurring during the third week, although at times delayed for as long as 25 days. By the thirtieth day, the count is usually within the normal range. Thrombocytopenia, Granulocytopenia and Pancytopenia also may occur. Some fatal outcomes have been reported in case of Granulocytopenia and Pancytopenia.

A low grade hemolytic-uremic state, exacerbated by blood transfusions, has been associated with long term therapy with fluorouracil with mitomycin-C.

Immune System Disorders
Anaphylactic reaction and Hypersensitivity.Some fatal outcomes have been reported in patient treated with multiple chemotherapy regimens.

Metabolism and Nutrition Disorders
Dehydration

Psychiatric Disorders
Confusional state, Disorientation, Euphoric mood

Vascular Disorders
Haemorrhage,Thrombophlebitis. Some fatal outcomes have been reported in case of haemorrhage.

Gastrointestinal effects
Anorexia and nausea are some of the earliest untoward symptoms during a course of therapy and generally occur during the first week. Those reactions are followed shortly after by stomatitis and diarrhea, which constitute reliable warning signals that sufficient dose has been administered. Esophagitis has also been reported. A Mallory-Weiss lesion following intravenous fluorouracil in combination chemotherapy has also been observed. Gastrointestinal

haemorrhage, Gastrointestinal ulcer, Melaena have been reported. Some fatal outcomes have been reported in case of gastrointestinal haemorrhage.

Dermatological effects
Alopecia and dermatitis are seen in a substantial number of cases and patients should be advised of this consequence of treatment. The alopecia is reversible. The dermatitis is often a pruritic maculopapular rash generally appearing on the extremities and less frequently on the trunk. It is usually reversible and responsive to symptomatic treatment. Dry skin and fissuring have also been noted.

The administration of fluorouracil has been associated with the occurrence of palmar-plantar erythrodysesthesia syndrome, also known as hand-foot syndrome. Continuous-infusion fluorouracil may increase the incidence and severity of palmar-plantar erythrodysesthesia. This syndrome has been characterized as a tingling sensation of hands and feet, which may progress over the next few days to pain when holding objects or walking. The palms and soles become symmetrically swollen and erythematous with tenderness of the distal phalanges, possibly accompanied by desquamation. Interruption of therapy is followed by gradual resolution over 5 to 7 days. Supplementation of chemotherapy with oral pyridoxine has been reported to prevent or resolve such symptoms.

Photosensitivity, manifested by erythema or increased skin pigmentation, and nail changes including banding or loss of nails and vein discoloration proximal to injection sites may occasionally occur.

Neurological effects
Some sporadic cases of leukoencephalopathy have been reported with the onset of various neurological symptoms, such as decreased alertness, agitation and disorientation memory deficit. Usually the leukoencephalopathy are resolved favorably within a few days of fluorouracil discontinuation. Headache and Nystagmus have been reported.

Eye Disorders
Photophobia, Visual impairment and Dacryostenosis acquired have been reported.

Cardiac effects
Cardiac shock, cardiac failure, cardiomyopathy, myocarditis, Pericarditis, angina, ECG abnormalities and myocardial infarction have been reported after administration of fluorouracil. Attention should therefore be paid to patients who experience chest pain during treatment, and patients with a history of heart disease.

Other adverse effects
Chest pain, which ranges from mild angina to crushing pain indistinguishable from that of myocardial infarction, has been reported. This may reoccur with subsequent doses of fluorouracil. Pyrexia has been reported.

Fewer than one percent of patients receiving fluorouracil will have ataxia or other manifestations of acute cerebellar syndrome due to drug neurotoxicity, although the incidence increases when

high doses or intensive daily regimes are used. The dysfunction is completely reversible and may not occur when the drug is re-introduced. Oculomotor disturbances expressed primarily as weakness of convergence and divergence, associated with neurotoxicity, have been noted.

Excessive lacrimation, which gradually appears after fluorouracil treatment and persists throughout treatment with the drug, has been reported.

Investigations
Electrocardiogram change; some fatal outcomes have been reported.

Reporting Suspected 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* (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Daily doses of fluorouracil of 30 mg/kg/day (1.1 to 1.2 g/m^2/day) by 5 day continuous infusion have been tolerated. At 35 mg/kg/day, seven out of eight patients developed severe stomatitis.

Administration of fluorouracil should be discontinued promptly on the occurrence of stomatitis or esopharyngitis, leukopenia or rapidly falling WBC count, thrombocytopenia, intractable vomiting, diarrhea, gastrointestinal ulceration and bleeding or hemorrhage (see **PRECAUTIONS**).

Nausea and vomiting may be alleviated by antiemetics. Chronic overdosage may give rise to serious myelosuppression. Daily hematological evaluation should be performed to prevent overdosage. 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. Transfusions of blood or platelets should be given at any sign of hemorrhage. Patients should be carefully observed for intercurrent infection and if present, appropriate antibiotic therapy should be instituted promptly.

DOSAGE AND ADMINISTRATION

Patient selection

In order to be considered for fluorouracil therapy, a prospective patient should satisfy the following conditions:

1. Good dietary intake with no protein loss
2. No major surgery within the past 30 days
3. No history of high dose irradiation to bone-marrow bearing areas of the body (pelvis, spine, ribs, etc.)
4. Good or adequate marrow recovery after prior use of a myelosuppressive regime
5. No serious infections
6. Adequate renal and hepatic functions
7. Adequate bone marrow function (leukocyte count 5,000/mm^3 or over; platelet count 100,000/mm^3 or over)

General dosage and administration recommendations

Fluorouracil Injection USP may be administered by intravenous infusion or intravenous injection, taking care to avoid extravasation. No dilution of Fluorouracil Injection USP is required when given by direct intravenous injection. Dosage is normally based on the patient's weight. However, if the patient is obese or there has been a spurious weight gain because of edema, ascites or other forms of abnormal fluid retention, the ideal weight or estimated lean body mass should be used.

In order to obtain optimum therapeutic results with minimal adverse effects, dosage must be based on the clinical and hematologic response and tolerance of the patient. It is thus recommended that each patient be carefully evaluated prior to therapy to estimate accurately the optimum initial dosage of fluorouracil.

Initial therapy

(See **CONTRAINDICATIONS, WARNINGS** and **PRECAUTIONS**). 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". Therapy should be discontinued promptly when any of the signs of toxicity listed under **PRECAUTIONS** appears.

Administration by infusion may result in slightly less toxicity. Diluted solutions (see **PHARMACEUTICAL INFORMATION: Dilution for Infusion Solutions**) of Fluorouracil Injection USP 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/m^2/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.

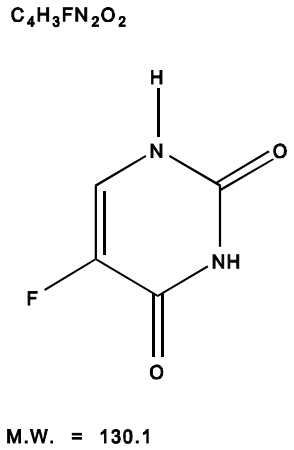
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Fluorouracil (5-FU)

Chemical Name: 2,4 (1H, 3H)-pyrimidinedione, 5-fluoro-5-fluorouracil

Chemical Structure:



Molecular Formula: $C_4H_3FN_2O_2$

Molecular Weight: 130.08 g/mol

Description: Fluorouracil is a white to practically white, practically odorless, crystalline powder. It decomposes at about 282°C. It is sparingly soluble in water, slightly soluble in alcohol and practically insoluble in chloroform and in ether.

Composition: Fluorouracil Injection USP (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 8.6 - 9.4 with sodium hydroxide.

Stability and Storage Recommendations

Store unopened vials of Fluorouracil Injection USP (50 mg/mL) between 15°C and 25°C. Protect from light and freezing.

The product is available in a clear glass vial that is packaged in an ONCO-TAIN® (clear plastic polyethylene terephthalate) sleeve to protect from breakage. It is recommended that the vial remains in the carton until time of use. The Fluorouracil Injection USP 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.

Dilution for Infusion Solutions

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 USP (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.

Fluorouracil Injection USP (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.

SPECIAL INSTRUCTIONS FOR HANDLING OF CYTOTOXIC DRUGS

The following are precautionary measures recommended in the handling and preparation of cytotoxic agents such as fluorouracil:

1. The procedure should be carried out in a vertical laminar flow hood (Biological Safety Cabinet - Class II).

2. Fluorouracil is an irritant and care should be taken to avoid contact with the skin and mucous membranes. It is thus recommended that personnel wear PVC gloves, safety glasses, disposable gowns and masks when carrying out dilutions of fluorouracil.

3. All vials, syringes, needles and other materials which have come in contact with fluorouracil should be segregated and destroyed by incineration. Sealed containers may explode if a tight seal exists. If incineration is unavailable, neutralization using 0.1M sodium hydroxide solution or 5% sodium hypochlorite (household bleach) should be carried out instead.

4. Bi-annual hematologic examinations should be performed on personnel regularly involved in the handling and preparation of fluorouracil.

Adsorption to administration equipment
The stability of fluorouracil is greater in plastic containers than in low grade glass containers due to adsorption of the drug to glass surfaces. It is suggested that deactivated glass surfaces such as those found in silanized glass be used to prevent drug loss due to adsorption.

Fluorouracil does not adsorb to PVC tubing, polyethylene tubing, silastic tubing, polypropylene barrels or polyethylene plungers of plastic syringes.

AVAILABILITY OF DOSAGE FORM

Fluorouracil Injection USP (50 mg/mL) is available as a 5 g/100 mL sterile, unpreserved solution in pharmacy bulk ONCO-TAIN® vials (single packs).

PHARMACOLOGY

Cell culture studies

The mechanism of cytotoxicity produced by fluorouracil is associated with both RNA and DNA directed effects depending on the tumour cell line. The pretreatment of mouse lymphocytes with fluorouracil prevented these cells from passing from the G_1 phase to the S phase of the cell cycle, thereby inhibiting replication of their DNA and causing extensive DNA strand breakage. Non-toxic concentrations were capable of synchronizing and increasing the fraction of cells in the drug-sensitive S phase. Enhancement of fluorouracil cytotoxicity was demonstrated in Hela cells synchronized by the double thymidine block method and treated with the drug during the DNA synthetic phase. The antitumour activity of the drug increased with exposure time. Metabolic phosphorylation of fluorouracil was faster in tumour tissue than in normal tissue.

Animal studies

In rats with transplanted colon tumour, a seven-day IV infusion of fluorouracil (25 to 35 mg/kg/day) produced a 30 to 70% tumour-free cure, while daily IV bolus injections of the drug (25 mg/kg/day) for seven days gave 80 to 100% cures with no apparent drug toxicity. A concentration-effect relationship was observed in the 7-day fluorouracil infusion, where the cure rate increased from 30 to 80%, when the steady-state concentration of the drug was increased from 136 ng/mL at a dose of 25 mg/kg/day to 240 ng/mL at 35 mg/kg/day. Further increases to 331 ng/mL at 50 mg/kg/day led to severe drug toxicity. At the dosages employed, the disposition of fluorouracil was described by non-linear kinetics, the blood clearance dependent on the route of administration as well as infusion rate, with clearances increasing at slower drug administration rates.

Clinical studies

No definitive effect of fluorouracil on the immune functions of 12 patients suffering from disseminated cancer was seen, as evidenced by the T or B cell numbers, B cell function, serum immunoglobulin levels or by ABO antibody titres. However, the drug appeared to affect the function of T cells.

TOXICITY

Acute toxicity

Species	Number	Route	Mean LD50	Sex
Mouse	3 to 6	I.P	340 mg/kg	F
Guinea Pig	5	IV	25.5 mg/kg	M

Subacute toxicity

Mice were given I.P. injections of 33, 66, 134 and 200 mg/kg of fluorouracil daily for 1, 2, 3 or 4 consecutive days. Groups of five mice from each schedule and dose level were evaluated hematologically, histologically and biochemically on post-treatment days 1, 3, 6, 10, 14 and 21.

The LD_{10}'s for the 1, 2, 3 and 4 sequential daily doses were 200, 162, 61 and 39 mg/kg/dose respectively.

Reticulocyte counts revealed suppression of marrow production within 2 days of the initial dose, followed by a dose-dependent delay in return to normal reticulocyte counts. An erythrocyte nadir occurred on day 10 post-treatment. Peripheral leukopenia was characterized by both granulocytopenia and lymphopenia. Severity and time to recover were dose related.

Myeloid:erythroid (M:E) ratios were affected by fluorouracil treatment. The M:E ratio was higher than normal on day 1 of treatment, but reversed after about day 6, indicating resumption of erythroid and myeloid proliferation.

A dose dependent loss of body weight of from 6 to 22%, reached a nadir on Day 3, and was independent of schedule. All survivors recovered their lost weight by day 21.

Clinical chemistry effects were unremarkable.

Injury to the gastrointestinal tract was the most consistent drug dependent lesion disclosed by histologic examination. A single dose of fluorouracil produced a transient episode of mild intestinal epithelial change on day 3. After three sequential doses, toxicity was clearly dose dependent, as manifested by the extent and severity of epithelial hyperplasia and villar atrophy in the small intestine. Lesions were observed in 0, 20, 40, 80, and 100% of animals receiving 0, 33, 66, 134, and 200 mg/kg of fluorouracil, respectively, in three sequential daily doses.

Cardiac studies

Anesthetized open-chest guinea pigs showed ECG changes indicative of ischemia after intravenous administration of fluorouracil. The incidence of ECG abnormality at 3 hours in seven animals given 60 mg/kg was 100%, while that in animals given 30 mg/kg was 44% (four of nine animals). With 10 to 20 mg/kg, ECG changes were not observed. A depletion of the high-energy phosphate compounds of the ventricular myocardium observed from tissue biochemistry studies, reflected drug related interference in the tricarboxylic acid cycle.

Reproductive toxicity

The teratogenic effect of fluorouracil was studied in chicken embryos during the first four days of development. The yolk sac injection of the drug produced specific and reproducible developmental anomalies, which varied with the time of injection.

Teratological effects were observed in hamster fetuses when the mother received a single I.M. injection of fluorouracil (3 to 9 mg) between days 8 and 11 of gestation. The malformation rate was related to the dose and time of drug administration. As organogenesis advanced, higher doses of fluorouracil were required to produce malformed embryos. The overall malformation rate was highest on day 9 (78%). Fluorouracil was highly toxic to the embryo between days 8 and 11 of gestation with high resorption rates on days 9 to 11.

Pregnant albino mice were administered 40 mg/kg fluorouracil I.P. on day 10 of gestation producing 96.3% embryo lethality and 100% surviving fetal malformations.

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