

**FLUOROURACIL**  
Fluorouracil Injection BP 25mg/ml

### **Composition**

Fluorouracil Injection BP is a sterile, colourless, isotonic, preservative-free solution containing Fluorouracil BP 25mg/mL and Sodium Hydroxide BP (for pH adjustment) in Water for Injections BP.

### **Pharmacology**

#### *Class*

Antineoplastic agent.

#### *Mechanism of action*

Fluorouracil is an analogue of uracil and is an antimetabolite. Fluorouracil itself is inactive, but following intracellular conversion to active metabolites it interferes with the synthesis of DNA and also RNA. It acts by blocking the conversion of deoxyuridylic acid to thymidylic acid by inhibiting the enzyme thymidylate synthetase. This creates a thymidine deficiency resulting in cell death, especially in rapidly dividing cells which preferentially take up fluorouracil.

### **Pharmacokinetics**

Following intravenous infusion, fluorouracil is distributed into tumours, intestinal mucosa, bone marrow, liver and other tissues throughout the body. It readily crosses the blood-brain barrier and distributes into the cerebrospinal fluid.

Fluorouracil is metabolised primarily in the liver. The degradation products are inactive and non-toxic. The plasma half-life of fluorouracil ranges from 8-22 minutes and is dose dependent.

Less than 20% of a single intravenous dose of fluorouracil is excreted unchanged in the urine within six hours.

### **Indications**

For the palliative treatment, either alone or in combination of malignant tumours particularly of the breast, colon, and rectum. It is also used for the treatment of gastric, primary hepatic, pancreatic, uterine, ovarian, and bladder carcinomas.

**Breast cancer:** Fluorouracil has been used as part of combination therapy as an adjunct to surgery in the treatment of early breast cancer in women with negative axillary lymph nodes and oestrogen receptor negative tumours.

Fluorouracil has also been used to treat more advanced forms of breast cancer including inoperable cancer.

**Gastrointestinal cancer:** Fluorouracil, when used as an adjunct to surgery, has produced temporary improvement in a substantial number of patients with advanced carcinoma of the gastrointestinal tract.

### **Contraindications**

- Known hypersensitivity to fluorouracil.
- Poor nutritional state.
- Depressed bone marrow function (leukocyte count less than 5,000/mm<sup>3</sup>, platelet count less than 100,000/mm<sup>3</sup>).
- Potentially serious infection.
- Pregnancy.

### **Warnings and Precautions**

*Fluorouracil should be administered only under constant supervision by physicians experienced in therapy with cytotoxic agents and only when the potential benefits of fluorouracil therapy outweigh the possible risks.*

*Because of the possibility of severe toxic reactions, appropriate facilities should be available for adequate management of complications should they arise.*

- **Toxicity:** Fluorouracil has a narrow margin of safety and is a highly toxic drug. Fluorouracil therapy should be discontinued promptly whenever one of the following signs of toxicity appears: stomatitis, oesophagopharyngitis, intractable vomiting, diarrhoea, haemorrhage, oral ulceration, evidence of gastrointestinal ulceration or bleeding.  
Any form of therapy that adds to the stress of the patient, interferes with nutritional uptake or depresses bone marrow function will increase the toxicity of fluorouracil.
- **Myelosuppression:** Leucopenia and thrombocytopenia commonly follow treatment with fluorouracil. Daily monitoring of platelet and white blood cell counts is recommended. Treatment with fluorouracil should be discontinued if the leucocyte count falls rapidly or if it falls below  $3,500/\text{mm}^3$ , or if there is a fall in the platelet count below  $100,000/\text{mm}^3$ . If the leucocyte count falls below  $2,000/\text{mm}^3$  the patient should be placed in an isolation unit and given an appropriate preventative treatment for systemic infection.
- **Cardiotoxicity:** There is an increased risk of death associated with re-administration of fluorouracil in patients with a documented cardiovascular reaction to fluorouracil (see Adverse Effects).
- **Combination chemotherapy/radiotherapy:** Extreme caution is necessary when administering fluorouracil to patients who have had high dose pelvic irradiation, or have previously been treated with alkylating agents. Concomitant use of other chemotherapeutic agents may depress bone marrow function and increase the toxicity of fluorouracil.
- **Renal and hepatic impairment:** Caution is necessary when administering fluorouracil to patients with renal and/or hepatic dysfunction.

#### *Use in the elderly*

Fluorouracil should be used with caution in the elderly. Age 70 years or older and female sex are statistically significant risk factors for severe toxicity from fluorouracil based chemotherapy. These effects may be additive in older women.

While advanced age does not contraindicate the use of this type of chemotherapy, close monitoring for multiple organ toxicities and vigorous supportive care of those with toxicity are required.

#### *Use in pregnancy*

**Category D.** Safety for use in pregnancy has not been established. Fluorouracil should only be used in women of child-bearing potential if the expected benefits outweigh the risks of therapy, and adequate contraception is used. If the patient becomes pregnant whilst receiving the drug she should be advised of the potential hazards to the fetus.

#### *Use in lactation*

It is not known whether fluorouracil is excreted in breast milk so breastfeeding should be discontinued during fluorouracil therapy in lactating women.

## **Drug Interactions**

Leucovorin (folinic acid) enhances the DNA-directed toxicity of fluorouracil. This combination should be used with caution as it is reported to increase the gastrointestinal toxicity of fluorouracil.

Allopurinol may decrease the degree of bone marrow depression produced by fluorouracil. Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of fluorouracil. Common drugs include methotrexate, metronidazole and leucovorin.

Pretreatment with cimetidine prior to intravenous fluorouracil increased the area under the curve by 27%. The total body clearance was reduced by 28%.

#### *Incompatibilities*

Admixtures with acidic drugs or drugs that are unstable in the presence of alkali should be avoided.

### *Effects on laboratory tests*

Fluorouracil could interfere with diagnostic tests of thyroid function by causing rises in total thyroxine and liothyronine due to increased globulin binding. Plasma albumin may be decreased because of drug-induced protein malabsorption.

### **Adverse Effects**

The ratio between effective and toxic dose is small and therapy with fluorouracil is usually accompanied by some degree of adverse effects. Patients should be carefully observed and dosage adjustment may have to be made. Deaths have been reported.

- **Gastrointestinal:** The most pronounced and dose-limiting toxic effects of fluorouracil are on the normal, rapidly proliferating tissues of the bone marrow and the lining of the gastrointestinal tract. Nausea and vomiting occur and may be treated symptomatically. Stomatitis is usually an early sign of impending severe toxicity which may become evident after 5-8 days of therapy. Symptoms include soreness, erythema or ulceration of the oral cavity or dysphagia. Other reported gastrointestinal symptoms are diarrhoea, proctitis and oesophagitis, therefore, the dose may require adjustment or therapy may need to be discontinued. Gastrointestinal side effects may be exacerbated if fluorouracil is given with folic acid.
- **Haematological:** Leucopenia, primarily granulocytopenia, commonly occurs. The nadir for white blood cell count usually occurs from the ninth to the fourteenth day after initiation of therapy, but may occur as late as the twenty-fifth day. The count usually returns to normal by the 30<sup>th</sup> day. Thrombocytopenia may also occur, with the lowest platelet counts occurring from the seventh to the seventeenth day of therapy.
- **Dermatological:** Alopecia may be seen in some individual cases, but it is reversible. Partial loss of nails, dermatitis and hyperpigmentation of the nail beds and other body areas have been reported. Skin rashes have been associated with fluorouracil therapy. Palmar-plantar erythrodysesthesia syndrome, thrombophlebitis and asymptomatic hyperpigmentation over vascular channels have also been reported.
- **Neurotoxicity:** Neurotoxicity may be evidenced by disorientation, confusion, euphoria, ataxia, dizziness, headache, muscular weakness, nystagmus, slurred speech, unsteadiness and acute cerebellar syndrome. These symptoms may persist after therapy is discontinued.
- **Cardiovascular:** Fluorouracil administration has, on occasion, been associated with angina, myocardial ischaemia, myocardial infarction, cardiomyopathy and, very rarely, sudden death. There have been reports of chest pain, tachycardia, breathlessness, arrhythmia, and ECG changes (ST segment changes) after administration of fluorouracil.
- **Ophthalmic:** Systemic fluorouracil treatment has been associated with various types of ocular toxicity. Excessive lacrimation, dacryostenosis, visual changes and photophobia have also been reported.
- **Neurological:** Combination therapy with 5-fluorouracil and levamisole has been associated with multifocal inflammatory leucoencephalopathy (MILE). Symptoms may include memory loss, confusion, paraesthesia, lethargy, muscle weakness, speech disturbances, coma and seizures. The cerebrospinal fluid may show mild pleiocytosis, and computed tomography and magnetic resonance scans may show lesions in the white matter suggestive of demyelination. If this syndrome occurs, treatment should be discontinued immediately. The condition is at least partially reversible if 5-fluorouracil and levamisole are discontinued and corticosteroids given.
- **Other:** Fever. Rarely, anaphylaxis or generalised allergic reactions have occurred in patients receiving fluorouracil.

### **Dosage and Administration**

Fluorouracil Injection BP may be administered by intravenous injection or infusion and the dosage should be based on the patient's actual weight. Ideal weight should only be used in obese patients or in those who have had a spurious weight gain due to oedema, ascites or other forms of abnormal fluid retention. Prior to treatment each patient is to be carefully evaluated in order to estimate the optimum initial dosage of fluorouracil. ***The total daily dose of fluorouracil should not exceed 1g.*** The initial recommended doses should be reduced by one third to a half for the following conditions: poor nutritional state; within 30 days after major surgery; inadequate bone marrow function (white blood cell count <5,000/mm<sup>3</sup>, platelet count <100,000/mm<sup>3</sup>) or impaired hepatic and/or renal function.

**Intravenous infusion:** 15mg/kg bodyweight (to a maximum of 1g) daily in 300-500mL of 5% glucose and given over a period of four hours. Infusions should be continued daily until the first side effects occur, i.e. stomatitis, diarrhoea, leucopenia and thrombocytopenia; treatment is then discontinued. After the side effects have subsided and white blood cell count has risen to 3,000-4,000/mm<sup>3</sup> or platelets to 80,000-100,000/mm<sup>3</sup>, the patient should receive maintenance therapy.

**Intravenous injection:** 12mg/kg bodyweight daily for three consecutive days. If toxic effects do not appear, 6mg/kg may be given intravenously on the fifth, seventh and ninth days. If there are still no signs of toxicity, the patient may receive maintenance therapy, otherwise regression of toxic side effects must be awaited before continuing therapy.

**Maintenance therapy:** 5-10mg/kg bodyweight by intravenous injection once a week. Toxic effects rarely occur during maintenance therapy. If, however, they do appear, therapy must be discontinued until the symptoms regress.

**Other methods of administration:** Fluorouracil may be given in combination with other cytostatic agents or radiotherapy; in such cases doses should be reduced accordingly. Administration of 5-7mg/kg daily may also be performed as a 24 hour intra-arterial continuous drip infusion.

### Overdosage

The possibility of overdosage with fluorouracil is unlikely in view of the mode of administration. Symptoms include nausea, vomiting, diarrhoea, gastrointestinal ulceration and bleeding and bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). No specific antidotal therapy exists. Patients who have been exposed to an overdose of fluorouracil should be monitored haematologically for at least four weeks. Should abnormalities appear, appropriate therapy should be utilised.

### Handling Precautions

As with all antineoplastic agents, trained personnel should prepare Fluorouracil Injection BP. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling fluorouracil. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as fluorouracil.

Luer-Lock fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Items used to prepare Fluorouracil Injection BP, or articles associated with body waste should be disposed of by placing in a double sealed polythene bag, and incinerating at 1100°C.

### Spills and Disposal

If spills occur, restrict access to the affected area. Wear two pairs of gloves (latex rubber), a respirator mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towel or adsorbent granules. Spills may also be treated with 5% sodium hypochlorite. Collect up absorbent/adsorbent material and other debris from spill and place in a leak proof plastic container and label accordingly. Cytotoxic waste should be regarded as hazardous or toxic and clearly labelled 'CYTOTOXIC WASTE FOR INCINERATION AT 1100°C'. Waste material should be incinerated at 1100°C for at least 1 second. Cleanse the remaining spill area with copious amounts of water.

### Presentation

Fluorouracil Injection BP 250mg/10mL (sterile) Plastic Vial (5's) [Non-marketed].

Fluorouracil Injection BP 500mg/20mL (sterile) Plastic Vial (5's).

Fluorouracil Injection BP 2500mg/100mL (sterile) Plastic Vial.

### Storage

Store between 15 - 25°C. Do not refrigerate. Protect from light. Single use only. Discard unused portion.

The expiry date (month/year) is stated on the package after EXP.

## **Medicine Classification**

Prescription Medicine

## **Further Information**

*Carcinogenicity, mutagenicity and impairment of fertility*

**Carcinogenicity:** Long term studies in animals to evaluate the carcinogenic potential of fluorouracil have not been conducted. However, there was no evidence of carcinogenicity in small groups of rats given fluorouracil orally at doses of 0.01, 0.3, 1 or 3mg per rat 5 days per week for 52 weeks, followed by a 6 month observation period. On the basis of the available data, no evaluation can be made of the carcinogenic risk of fluorouracil to humans.

**Mutagenicity:** Oncogenic transformation of fibroblasts from mouse embryo has been induced in vitro by fluorouracil, but the relationship between oncogenicity and mutagenicity is not clear. A positive effect was observed in the micronucleus test on bone marrow cells of the mouse, and fluorouracil at very high concentrations produced chromosomal breaks in hamster fibroblasts in vitro.

**Impairment of fertility:** 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 250mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosomal organisation of spermatogonia in rats.

Spermatogonial differentiation was also inhibited by 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, fluorouracil did not produce any abnormalities at oral doses of up to 80mg/kg/day. In female rats, fluorouracil, administered intraperitoneally at weekly doses of 25 or 50mg/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 a limited study in rabbits, a single 25mg/kg dose of fluorouracil or 5 daily doses of 5mg/kg had no effect on ovulation, appeared not to affect implantation and had only a limited effect in producing zygote destruction. Compounds such as fluorouracil, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on gametogenesis.

In general, use of a contraceptive is recommended during cytotoxic drug therapy.

## **Name and Address**

Pfizer New Zealand Limited  
Level 3, Pfizer House  
14 Normanby Road  
Mt Eden  
Auckland  
New Zealand

Ph: (09) 638 0000

## **Date of Preparation**

16 January 2004 (Ref.: Aust PI dated 8 January 2002).