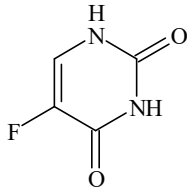
# PRODUCT INFORMATION
# FLUOROURACIL INJECTION BP

## NAME OF THE MEDICINE

Fluorouracil Injection BP (fluorouracil) 25 mg

Fluorouracil is 5-fluoro-1H,3H-pyrimidine-2,4-dione and has the structural formula shown below:




Molecular Formula: $C_4H_3FN_2O_2$
Molecular Weight: 130.1
CAS Registry Number: 51-21-8.

## DESCRIPTION

Fluorouracil is a white or almost white, crystalline powder which is sparingly soluble in water, slightly soluble in alcohol and practically insoluble in ether.
Fluorouracil Injection BP is a sterile, colourless, isotonic, preservative-free solution containing fluorouracil 25 mg/mL and sodium hydroxide (for pH adjustment) in Water for Injections.

## PHARMACOLOGY

**Pharmacodynamics**
***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 of the breast, colon, rectum, stomach or pancreas.

**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 or its excipients.
• Poor nutritional state.
•Depressed bone marrow function (leucocyte count less than 5,000/$mm^3$, platelet count less than 100,000/$mm^3$).
• Potentially serious infection.
• Pregnancy.

Fluorouracil 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 INTERACTIONS WITH OTHER MEDICINES).

## 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. 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. Fluorouracil therapy should be discontinued promptly whenever one of the following signs of toxicity appears: leucopenia, thrombocytopenia, stomatitis, oesophagopharyngitis, intractable vomiting, diarrhoea, melena, 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**
Cytotoxic agents, including fluorouracil, may produce myelosuppression (including, but not limited to, leucopenia, granulocytopenia, pancytopenia and thrombocytopenia). Leucopenia, primarily granulocytopenia, and thrombocytopenia commonly follow treatment with fluorouracil.

Treatment should not be started in the presence of diminished leucocytes and/or platelets and the dose should be reduced if these conditions develop during treatment (see CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

Leucopenia occurs after nearly every treatment period with an effective dose. The nadir for white blood cell count usually occurs from the $9^{th}$ to the $14^{th}$ day after initiation of therapy, but may occur as late as the $25^{th}$ day. The count usually returns to normal by the $30^{th}$ day. Thrombocytopenia may also occur, with the lowest platelet counts occurring from the $7^{th}$ to the $17^{th}$ day of therapy.

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/$mm^3$, or if there is a fall in the platelet count below 100,000/$mm^3$. If the leucocyte count falls below 2,000/$mm^3$ the patient should be placed in an isolation unit and given an appropriate preventative treatment for systemic infection.

Clinical consequences of severe myelosuppression include infections. Viral, bacterial, fungal and/or parasitic infections, either localised 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.

**Cardiotoxicity**
Fluorouracil administration has 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. Attention should therefore be paid to patients who experience chest pain during treatment, and patients with a history of heart disease. There is an increased risk of death associated with re-administration of fluorouracil in patients with a documented cardiovascular reaction to fluorouracil.

**Special Risk Patients and 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, and in those who have a widespread involvement of bone marrow by metastatic tumours. Radiation therapy on the bone marrow, especially to the area of the chest and mediastinum, may potentiate the bone marrow effects of fluorouracil. Fluorouracil treatment may potentiate necrosis caused by radiation. 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 (see DOSAGE AND ADMINISTRATION).

**Dihydropyrimidine Dehydrogenase Deficiency**
Rarely, severe toxicity (e.g. stomatitis, diarrhoea, neutropenia, and neurotoxicity) associated with fluorouracil has been attributed to 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.

**Gastrointestinal Effects**
Loss of appetite, nausea and vomiting occur and may be treated symptomatically. Stomatitis is usually an early sign of impending severe toxicity which may become evident as early as the fourth day, but more commonly appears 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. Diarrhoea is usually mild but it may sometimes be severe and may occur later in treatment. Severe diarrhoea may also be accompanied by dehydration and melaena. Gastrointestinal side effects may be exacerbated if fluorouracil is given with folinic acid.

**Hand-Foot Syndrome**
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 characterised 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.

**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.

**Multifocal Inflammatory Leucoencephalopathy (MILE)**
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.

**Paediatric Use**
Safety and effectiveness have not been established.

**Use in the Elderly**
Fluorouracil should be used with caution in elderly patients. 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**
Australian Category D.

Teratogenic effects have been detected in animal studies and fluorouracil can be considered an agent that can cause foetal malformations. Fluorouracil is therefore contraindicated during pregnancy (see CONTRAINDICATIONS). Women of childbearing age should be advised to avoid pregnancy during fluorouracil therapy. 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 receives fluorouracil during pregnancy or becomes pregnant whilst receiving the drug she should be advised of the potential hazards to the foetus.

Compounds such as fluorouracil, which interfere with DNA, RNA and protein synthesis, might be expected to have adverse effects on gametogenesis. Men undergoing fluorouracil treatment should also ensure they use effective contraception measures.

Australian Category D: Drugs that have caused, are suspected to have caused - or may be expected to cause - an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

**Use in Lactation**
It is not known whether fluorouracil is excreted in breast milk so breast-feeding should be discontinued during fluorouracil therapy in lactating women.

**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 3 mg 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.

**Genotoxicity**
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.

**Effects on 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 250 mg/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 80 mg/kg/day. In female rats, 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 a limited study in rabbits, a single 25 mg/kg dose of 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.

**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.

## INTERACTIONS WITH OTHER MEDICINES

**Brivudine and Sorivudine**
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 hospitalisation is recommended.

**Cytotoxic Agents**
All myelosuppressive drugs (e.g. cytotoxic agents used in combination chemotherapy) can increase haematotoxicity of fluorouracil.

**Leucovorin (Folinic Acid)**
Leucovorin enhances the DNA-directed toxicity of fluorouracil. This combination should be used with caution as the toxicity of fluorouracil, especially GI and haematologic, may be increased. Careful monitoring should be observed and the dose of fluorouracil may be decreased based on current guidelines.

**Allopurinol**
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.

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

**Metronidazole**
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.

**Phenytoin**
Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with capecitabine or its metabolite fluorouracil. Formal interaction studies between phenytoin and capecitabine have not been conducted, but the mechanism of interaction is presumed to be inhibition of CYP2C9 isoenzyme system by capecitabine. Serum levels of phenytoin sustained above the optimal range may produce encephalopathy or confusional states (delirium psychosis) or rarely irreversible cerebellar dysfunction. Therefore, patients taking phenytoin concomitantly with capecitabine or fluorouracil should be regularly monitored for increased phenytoin plasma levels, and the phenytoin dosage may need to be reduced.

**Warfarin**
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.

**Live or Live-attenuated Vaccines**
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including fluorouracil, may result in serious or fatal infections (see PRECAUTIONS).

## ADVERSE EFFECTS

The ratio between effective and toxic dose is small and therapy with fluorouracil is usually accompanied by some degree of adverse effects. Adverse effects of fluorouracil mainly result from its effects on rapidly dividing cells of normal tissue and its effects on the gastrointestinal tract and haematopoietic systems (see PRECAUTIONS). Patients should be carefully observed and dosage adjustment may have to be made. Deaths have been reported.

The reported adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100, rare (≥1/10,000 to <1/1,000), very rare (<10,000) and not known (cannot be estimated from available data).

**Infections and Infestations**
Very common: Infection.
Common: Sepsis.
Not known: Progressive multifocal leucoencephalopathy, septic shock, neutropenic sepsis, pneumonia, superinfection, urinary tract infection, device related infection, cellulitis, pharyngitis.

**Blood and Lymphatic System Disorders**
Very common: Bone marrow failure, leucopenia, thrombocytopenia.
Not known: Granulocytopenia, pancytopenia.

**Immune System Disorders**
Not known: Anaphylactic reaction, hypersensitivity.

**Metabolism and Nutrition Disorders**
Not known: Dehydration, decreased appetite.

**Psychiatric Disorders**
Not known: Confusional state, disorientation, euphoric mood.

**Nervous System Disorders[a]**
Not known: Cerebellar syndrome, ataxia, dizziness, dysarthria, headache, nystagmus.

**Eye Disorders**
Not known: Photophobia, visual impairment, lacrimation increased, dacryostenosis acquired.

**Cardiac Disorders**
Common: Myocardial infarction, myocardial ischaemia, angina pectoris[b], arrhythmia.
Not known: Cardiomyopathy, tachycardia.

**Vascular Disorders**
Not known: Haemorrhage, thrombophlebitis.

**Respiratory, Thoracic and Mediastinal Disorders**

Not known: Dyspnoea.

**Gastrointestinal Disorders**

Very common: Diarrhoea, stomatitis, vomiting, nausea.

Not known: Gastrointestinal haemorrhage, gastrointestinal ulcer, oesophagitis, melaena.

**Skin and Subcutaneous Tissue Disorders**

Very common: Alopecia[c].

Common: Palmar-plantar erythrodysaesthesia syndrome[d].

Not known: Dermatitis[e], photosensitivity reaction, rash, skin hyperpigmentation[f], skin fissures, dry skin, nail disorder[g], nail hyperpigmentation.

**Musculoskeletal and Connective Tissue Disorders**

Not known: Muscular weakness.

**General Disorders and Administration Site Conditions**

Not known: Sudden death, pyrexia, chest pain, injection site reaction.

**Investigations**

Common: Electrocardiogram change.

a Symptoms may persist after therapy is discontinued.

b Observed in patients receiving high dose leucovorin and 5-fluorouracil bolus and continuous infusion

c Reversible

d Observed in patients who received 5-fluorouracil and leucovorin bolus administration

e Manifests often as itchy maculopapular rash on the extremities

f Skin hyperpigmentation also refers to asymptomatic hyperpigmentation over vascular channels

g Such as partial or complete detachment of nails

## 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 1 g**. The initial recommended doses should be reduced by one third to a half for the following conditions: within 30 days after major surgery; or impaired hepatic and/or renal function. Should a poor nutritional state or inadequate bone marrow function (white blood cell count <5,000/$mm^3$, platelet count <100,000 $mm^3$) develop during treatment, the dose should also be similarly reduced in order to allow nutritional and bone marrow recovery.

**Intravenous Infusion**

15 mg/kg bodyweight (to a maximum of 1 g) daily in 300-500 mL 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/$mm^3$ or platelets to 80,000-100,000/$mm^3$, the patient should receive maintenance therapy.

**Intravenous Injection**

12 mg/kg bodyweight daily for three consecutive days. If toxic effects do not appear, 6 mg/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**
5-10 mg/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 5-7 mg/kg daily may also be performed as a 24 hour intra-arterial continuous drip infusion.

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

**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.

## OVERDOSAGE

The possibility of overdosage with fluorouracil is unlikely in view of the mode of administration. High dosages or prolonged treatment with fluorouracil can result in life-threatening intoxication symptoms. The anticipated symptoms of fluorouracil overdosage would include nausea, vomiting, diarrhoea, gastrointestinal ulceration and bleeding and bone marrow depression (including thrombocytopenia, leucopenia 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.

## PRESENTATION AND STORAGE CONDITIONS

Fluorouracil Injection BP 250 mg/10 mL (sterile) Plastic Vial (5's).
Fluorouracil Injection BP 500 mg/20 mL (sterile) Plastic Vial (5's).
Fluorouracil Injection BP 2.5 g/100 mL (sterile) Plastic Vial.
Not all presentations may be marketed.

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

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

## NAME AND ADDRESS OF THE SPONSOR

**Sponsor**
Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
West Ryde NSW 2114
Australia

**Manufacturer**
Pfizer (Perth) Pty Limited
ABN 32 051 824 956
15 Brodie Hall Drive,

Bentley WA 6102
Australia

**DATE OF MOST RECENT AMENDMENT**17 January 2017