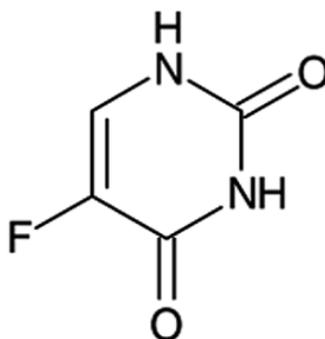


**PRODUCT INFORMATION****FLUOROURACIL EBEWE® 500MG/10ML, 1000MG/20ML, 2500MG/50ML,  
5000MG/100ML INJECTION SOLUTION****NAME OF THE MEDICINE**

Fluorouracil

**Composition***Active.* Fluorouracil.*Inactive.* Water for injections, sodium hydroxide.**Fluorouracil****DESCRIPTION**

Chemical name: 5-fluoro-1H, 3H-pyrimidine-2, 4-dione. C<sub>4</sub>H<sub>3</sub>FN<sub>2</sub>O<sub>2</sub>. MW: 130.1. CAS: 51-21-8. Fluorouracil is a white to almost white, practically odourless, crystalline powder. It is sparingly soluble in water, slightly soluble in alcohol and practically insoluble in chloroform and ether. The pH of the fluorouracil injection solution is approximately 8.9.

**PHARMACOLOGY**

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. Fluorouracil itself is inactive and is converted intracellularly to active metabolites. After conversion to the active deoxynucleotide, it interferes with the synthesis of DNA by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

Pharmacokinetics

After intravenous administration, fluorouracil is distributed throughout body tissues and fluids. The plasma half-life is 8 to 22 minutes and is dose dependent. Fluorouracil disappears from the blood within four hours. It is preferentially taken up by actively dividing tissues and

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tumours after conversion to its nucleotide. Fluorouracil readily enters the cerebrospinal fluid (CSF).

About 20% is excreted unchanged in the urine and the remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

## INDICATIONS

Alone or in combination, for the palliative treatment of malignant tumours, particularly of the breast, colon or rectum; and in the treatment of gastric, primary hepatic, pancreatic, uterine (cervical particularly), ovarian and bladder carcinomas.

Fluorouracil should only be used when other proven measures have failed or are considered impractical.

## CONTRAINDICATIONS

- who have any known hypersensitivity to fluorouracil,
- who are debilitated,
- who are suffering a poor nutritional state,
- who are suffering from bone marrow depression following radiotherapy or therapy with other antineoplastic agents (leucocyte count less than 5,000/mm<sup>3</sup>, platelet count less than 100,000/mm<sup>3</sup>),
- who are suffering from a potentially serious infection, and
- who are pregnant.

## PRECAUTIONS

Fluorouracil should be administered only by or under strict supervision of a qualified physician experienced in therapy with potent metabolites and only when the potential benefits of fluorouracil outweigh the possible risks. Because of the possibility of severe toxic reactions, all patients should be hospitalized, at least during the initial course of therapy and appropriate facilities should be available for adequate management of complications should they arise.

Rarely, severe and unexpected toxic reactions (including stomatitis, diarrhoea, neutropenia and neurotoxicity) have been reported in association with fluorouracil. These reactions have been attributed to deficiency of dipyrimidine dehydrogenase activity, which appears to cause prolonged clearance of fluorouracil.

Fluorouracil should not be re-administered after a documented cardiovascular reaction (arrhythmia, angina, ST segment changes) as there is a risk of sudden death

Fluorouracil should be used with caution in patients with reduced renal or liver function, jaundice or heart disease.

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**Adequate treatment with fluorouracil is usually followed by leucopenia, the lowest white blood cell (WBC) count commonly being observed between the 9th and 14th day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the 30th day.** 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: leucopenia, thrombocytopenia, stomatitis, oesophagopharyngitis, intractable vomiting, diarrhoea, melaena, haemorrhage, oral ulceration, evidence of gastrointestinal ulceration or bleeding. Rarely, severe and unexpected toxic reactions (including stomatitis, diarrhoea, neutropenia and neurotoxicity) have been reported in association with fluorouracil. These reactions have been attributed to deficiency of dipyrimidine dehydrogenase activity, which appears to cause prolonged clearance of fluorouracil.

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.

The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken, therefore, in the selection of patients and adjustment of dosage.

#### 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).

#### Myelosuppression

Cytotoxic agents, including fluorouracil, may produce myelosuppression (including, but not limited to leucopenia, granulocytopenia, pancytopenia, and thrombocytopenia). Leucopenia and thrombocytopenia commonly follow treatment of 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.

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.

#### Combination Chemotherapy/Radiotherapy

Extreme caution is necessary when administering fluorouracil to patients who have had high dose pelvic irradiation or have been previously treated with alkylating agents. 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.

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### Impaired renal function

Fluorouracil should be used with caution in patients with reduced renal function or heart disease.

### Impaired hepatic function

Fluorouracil should be used with caution in patients with reduced liver function or jaundice.

### 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.

### Use in the elderly

Fluorouracil should be used with caution in elderly patients. An age of 70 years or older and the female gender 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.

### Carcinogenicity, Mutagenesis, Impairment of Fertility

**Carcinogenicity:** Long-term studies in animals to evaluate the carcinogenic potential of fluorouracil have not been performed. However, there was no evidence of carcinogenicity in small groups of rats given fluorouracil orally at doses 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.

**Mutagenicity:** Fluorouracil has been shown to be mutagenic and clastogenic in a number of studies. 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 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 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

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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. 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 therapy.

#### Use in pregnancy (Category D)

*Category D: Drugs which 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. Accompanying texts should be consulted for further details.*

Fluorouracil may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Fluorouracil administered parenterally has been shown to be teratogenic in mice, rats and hamsters, and embryolethal in monkeys. Fluorouracil is strictly contraindicated in pregnancy. 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 foetus.

Men undergoing fluorouracil treatment should also ensure they use effective contraception measures.

#### Use in lactation

It is not known whether fluorouracil is excreted in breast milk. To avoid possible harmful effects in the infant, breastfeeding is not advised during fluorouracil therapy.

#### Compatibilities

See **DOSAGE AND ADMINISTRATION**, Compatibilities.

#### Incompatibilities

Admixtures with acidic medicines or medicines that decompose in an alkaline environment should be avoided.

#### 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.

#### 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**

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

Folinic acid (leucovorin) 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. Studies of this possibility have reported conflicting results. Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of fluorouracil. Common medicines include methotrexate, metronidazole and folinic acid (leucovorin).

Combination therapy with 5-fluorouracil and levamisole has been associated with multifocal inflammatory leukoencephalopathy (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. The use of levamisole and 5-fluorouracil is no longer recommended by NH&MRC 'Clinical Practice guidelines: The prevention, early detection and management of colorectal cancer'. This combination regimen has been superseded by fluorouracil and folinic acid.

Pretreatment with cimetidine prior to intravenous fluorouracil increased the area under the concentration time curve (AUC) by 27%. The total body clearance was reduced by 28%. This may lead to increased plasma concentrations of fluorouracil.

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.

## **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 very 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 cells 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 be evident after five to eight days of therapy. Symptoms include soreness, erythema or ulceration of the oral

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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 folinic acid (leucovorin).

### Dermatological

Alopecia may be seen in a substantial number of 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. Continuous-infusion fluorouracil may increase incidence and severity of palmar-plantar erythrodysesthesia, photosensitivity reactions.

### Neurotoxicity

Neurotoxicity may be evidenced by disorientation, confusion, euphoria, ataxia, dizziness, headache, muscular weakness, nystagmus, slurred speech, unsteadiness and acute cerebellar syndrome and occasionally, oculomotor disturbances. These symptoms may persist after therapy is discontinued.

### 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 thirtieth day. Thrombocytopenia may also occur, with the lowest platelet counts occurring from the seventh to the seventeenth day of therapy.

### Cardiovascular

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.

### Ophthalmic

Systemic fluorouracil treatment has been associated with various types of ocular toxicity. Additionally, several other reports have been noted including excessive lacrimation, dacryostenosis, visual changes and photophobia.

### Neurological

Disorientation, confusion, euphoria, ataxia, nystagmus, headache, slurred speech, dizziness, unsteadiness, muscular weakness, acute cerebellar syndrome and occasionally oculomotor disturbances have occurred in patients receiving fluorouracil. These symptoms may persist after therapy is discontinued. 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

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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.

### Infections and Infestations

Septic shock, sepsis, neutropenic sepsis, pneumonia, superinfection, urinary tract infection, catheter related infection, cellulitis, pharyngitis, and other infections.

### Other

Local injection site reaction. Fever has also been reported. Rarely, anaphylaxis or generalised allergic reactions have occurred in patients receiving fluorouracil.

## DOSAGE AND ADMINISTRATION

### General Directions

Fluorouracil Ebewe contains no antimicrobial agent. The product is for single use in one patient only. Discard any residue.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours after preparation. Administration should be completed within 24 hours of preparation of the infusion and any residue discarded according to the guidelines for the disposal of cytotoxic drugs (see Handling Precautions, and Spills and Disposal, below).

Fluorouracil Injection may be administered by intravenous infusion or intravenous injection, the dosage being based on the patient's actual weight. Ideal weight is used only if the patient is obese or if there has been 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 one-half if any of the following conditions are present: 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>); impaired hepatic and/or renal function.

The following regimens have been recommended for use of fluorouracil as a single agent in adults.

### Intravenous Infusion

15 mg/kg bodyweight (to a maximum of 1g) daily diluted in 300 to 500 mL of glucose 5% given over a period of four hours. Infusions may be continued daily until the first gastrointestinal side effects occur, i.e. stomatitis, diarrhoea, leucopenia, thrombocytopenia; treatment should then be discontinued. After the side effects have subsided and the WBC count has risen to 3,000 to 4,000/mm<sup>3</sup> or the platelet count to 80,000 to 100,000/mm<sup>3</sup> the patient may then be placed on a maintenance therapy program.

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### Intravenous Injection

12 mg/kg bodyweight daily for three consecutive days. If toxic effects do not appear, the patient may then be given 6 mg/kg may be given intravenously on the 5th, 7th and 9th days. If there are still no signs of toxicity, the patients may be placed on maintenance therapy, otherwise regression of toxic side effects must be awaited before continuing therapy.

### Maintenance Therapy

5 to 10 mg/kg bodyweight by intravenous injection once a week. Toxic effects seldom occur during maintenance therapy. If, however, they do appear, therapy must be discontinued until the symptoms regress, otherwise regression of toxic side effects must be awaited before continuing therapy.

### Other Methods of Administration

Fluorouracil Ebewe may be used in combination with other cytostatic agents or with radiotherapy; in such cases, doses should be reduced accordingly. Administration of 5-7 mg/kg bodyweight daily may also be performed as a 24 hour intra-arterial continuous drip infusion.

### Compatibilities

Fluorouracil Ebewe is compatible with the following infusion media: 0.9% sodium chloride, 5% glucose, 0.9% sodium chloride with 5% glucose.

Fluorouracil Ebewe can be used in combination with other antitumour agents, but it is not recommended that it be mixed with these drugs in the same container.

## **OVERDOSAGE**

The possibility of overdose 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, 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.

Contact the Poisons Information Centre on (telephone Australia 13 11 26 or New Zealand 0800 POISON or 0800 764766) for advice on management of overdose.

## **Handling Precautions**

As with all antineoplastic agents, trained personnel should prepare Fluorouracil Ebewe. 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-Lok 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.

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Items used to prepare Fluorouracil Ebewe, or articles associated with body waste should be disposed of by placing in a double sealed polythene bag and incinerated at 1,100°C.

### **Spills and Disposal**

If spill occurs, restrict access to the affected area. Wear two pairs of latex rubber gloves, a suitable mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towels or adsorbent granules. Spills may also be treated with sodium hypochlorite 5%. Collect the absorbent/adsorbent and other debris from the spill and place in a leakproof plastic container and label accordingly. Cytotoxic waste should be regarded as toxic and hazardous and clearly labeled 'CYTOTOXIC WASTE FOR INCINERATION AT 1,100°C'. Waste material should be incinerated at 1,100°C for at least one second. Clean the remaining spill area with copious amounts of water.

### **PRESENTATION AND STORAGE CONDITIONS**

Fluorouracil Ebewe 500 mg/10 mL injection solution vial - glass vial: Pack of 1 and 5 vials

Fluorouracil Ebewe 1000 mg/20 mL injection solution vial - glass vial: Pack of 1 vial

Fluorouracil Ebewe 2500 mg/50 mL injection solution vial - glass vial: Pack of 1 vial

Fluorouracil Ebewe 5000 mg/100 mL injection solution vial - glass vial: Pack of 1 vial

*Not all presentations may be marketed in Australia*

Store below 25°C. Do not refrigerate. Do not freeze. Protect from light.

If a precipitate has formed as a result of exposure to low temperature, redissolve by heating to 60°C accompanied by vigorous shaking. Allow to cool to body temperature prior to use.

### **NAME AND ADDRESS OF SPONSOR**

Sandoz Pty Ltd

ABN 60 075 449 553

54 Waterloo Road

Macquarie Park, NSW 2113

Australia

Tel: 1800 634 500

### **POISON SCHEDULE**

S4- Prescription Only Medicine

### **Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):**

11 March 2011

**Date of most recent amendment:** 10/07/2017