DBL™ Fluorouracil Injection BP

1. NAME OF THE MEDICINE

Fluorouracil

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of DBL Fluorouracil Injection BP contains fluorouracil 25 mg or 50 mg.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

DBL Fluorouracil Injection BP is a sterile, colourless, preservative-free solution containing 5-Fluorouracil in Water for Injections, prepared with the aid of sodium hydroxide. The pH of the solution is approximately 8.9. DBL Fluorouracil Injection BP is a clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluorouracil is indicated 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.

4.2 Dose and method of administration

Dosage

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 gram.

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 1 g) daily diluted in 300 to 500 mL of 5% glucose given over a period of 4 hours. Infusion may be continued daily until the first gastrointestinal side effects occur, i.e. stomatitis, diarrhoea, leucopenia and thrombocytopenia, treatment must

be discontinued until the side effects have receded (until the WBC count has risen to 3,000 to 4,000 per mm^3 or platelet count to 80,000 to 100,000 per mm^3), the patient may then be placed on a maintenance therapy program.

Intravenous injection

12 mg/kg bodyweight daily for 3 consecutive days.

If toxic effects do not appear, the patient may then be given 6 mg/kg intravenously on the 5^{th}, 7^{th} and 9^{th} days. If there are still no signs of toxicity, the patient 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 symptoms seldom occur during maintenance therapy. If, however, they do appear, therapy must be discontinued until the symptoms resolve.

Dosage adjustments

The initial recommended doses should be reduced by one third to a half if any of the following conditions are present:

(1) poor nutritional state;

(2) after major surgery (within previous 30 days);

(3) inadequate bone marrow function (WBC count less than 5,000 per mm^3; platelet count less than 100,000 per mm^3);

(4) impaired hepatic and/or renal function.

Method of administration

DBL Fluorouracil Injection BP may be administered by intravenous infusion or intravenous injection.

Fluorouracil may be used in combination with other cytotoxic agents or with radiotherapy. In such cases doses should be correspondingly reduced. DBL Fluorouracil Injection BP may also be administered as a 24 hour intra-arterial continuous drip infusion (5 to 7.5 mg/kg bodyweight daily).

4.3 Contraindications

Fluorouracil is contraindicated in patients

- who have any known hypersensitivity to fluorouracil or its excipients,
- who are debilitated,
- who are suffering from 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^3, platelet count less than 100,000/mm^3),
- who are suffering from a potentially serious infection,
- who are pregnant, and
- with known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4 Special warnings and precautions for use).

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 section 4.5 Interactions with other medicines and other forms of interactions).

4.4 Special warnings and precautions for use

It is recommended that fluorouracil be given only by or under strict supervision of a qualified physician who is well acquainted with the use of potent antimetabolites. Because of the possibility of severe toxic reactions, all patients should be hospitalised, at least during the initial course of therapy.

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

Patients taking phenytoin concomitantly with fluorouracil should undergo regular testing because of the possibility of an elevated plasma level of phenytoin (see section 4.5 Interactions with other medicines and other forms of interactions).

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, melaena 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.

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.

Myelosuppression

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

The initial dose should be reduced, or treatment should not be started in the presence of diminished leucocytes and/or platelets (see sections 4.3 Contraindications and 4.2 Dose and method of administration).

Leucopenia occurs after nearly every treatment period with an effective dose. The nadir for white blood cell count usually occurs from the 9th to the 14th day after initiation of therapy, but may occur as late as the 20th day. The count usually returns to normal by the 30th day. Thrombocytopenia may also occur, with the lowest platelet counts occurring from the 7th to the 17th 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 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.

Cardiotoxicity

Fluorouracil administration has been associated with myocardial ischaemia, cardiomyopathy and, very rarely, sudden death. Angina, tachycardia, breathlessness, arrhythmia, ECG abnormalities, myocardial infarction and stress cardiomyopathy (Takotsubo Syndrome) 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. There is an increased risk of death associated with readministration of fluorouracil in patients with a documented cardiovascular reaction (see section 4.8 Adverse effects (undesirable effects)).

Combination chemotherapy/radiotherapy

May depress bone marrow function and increase the toxicity of fluorouracil. Extreme caution is necessary when administering fluorouracil to patients who have had high dose pelvic irradiation, or have been previously 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

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

Combination with phenytoin

Patients taking phenytoin concomitantly with fluorouracil should undergo regular testing because of the possibility of an elevated plasma level of phenytoin (see section 4.5 Interactions with other medicines and other forms of interactions).

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. DPD-deficiency related toxicity usually occurs during the first cycle of treatment or after dose increase. 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 before therapy through laboratory testing for the detection of total or partial DPD-deficiency, or when evaluating patients experiencing fluorouracil-related toxicities.

Patients with complete DPD-deficiency are at high risk of life-threatening or fatal toxicity and must not be treated with fluorouracil injection (see section 4.3 Contraindications). Patients with partial DPD-deficiency are at increased risk of severe and potentially life-threatening toxicity. A reduced starting dose should be considered to limit this toxicity. DPD-deficiency should be considered as a parameter to be taken into account in conjunction with other routine measures for dose reduction. Initial dose reduction may impact the efficacy of treatment. Consideration should be given to applicable clinical guidelines.

Gastrointestinal effects

Loss of appetite, nausea and vomiting are common adverse effects, which generally occur during the first week of therapy. These adverse effects may be treated symptomatically and can often be alleviated by antiemetics. 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 and occurs 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.

Photosensitivity reactions

Some patients may experience photosensitivity reactions following administration of fluorouracil, it is recommended that patients are warned to avoid prolonged exposure to sunlight (see section 4.8 Adverse effects (undesirable effects)).

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.

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 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.

Multifocal inflammatory leukoencephalopathy (MILE)

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 pleocytosis, 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.

Tumour lysis syndrome

Cases of tumour lysis syndrome associated with fluorouracil treatment have been reported from post-marketing sources. Patients at increased risk of tumour lysis syndrome (e.g., with renal impairment, hyperuricemia, high tumour burden, rapid progression) should be closely monitored. Preventive measures (e.g., hydration, correction of high uric acid levels) should be considered.

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 necessary.

Paediatric use

No data available.

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.

4.5 Interactions with other medicines and other forms of interactions

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

Folinic acid (Leucovorin). Leucovorin enhances the DNA-directed toxicity of fluorouracil. This combination should be used with caution as the toxicity of fluorouracil, especially gastrointestinal 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. Studies of this possibility have reported conflicting results.

Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of fluorouracil. Common drugs include methotrexate, metronidazole and folinic acid (leucovorin).

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.

Levamisole. Combination therapy with 5-fluorouracil and levamisole has been associated with multifocal inflammatory leukoencephalopathy (MILE). 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 (see section 4.4 Special warnings and precautions for use).

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

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 (see section 4.4 Special warnings and precautions for use).

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 section 4.3 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.

Radiation therapy. Radiation therapy on the bone marrow, especially to the area of the chest and mediastinum, may potentiate the bone marrow effects of fluorouracil.

Warfarin. Elevated international normalized ratio (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 section 4.4 Special warnings and precautions for use).

Laboratory values. Fluorouracil treatment may interfere with some laboratory tests. Increases in total serum thyroxine concentration (due to increased binding to globulin) have been reported.

4.6 Fertility, pregnancy and lactation

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.

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.

Use in pregnancy – Category D†

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 (see section 4.3 Contraindications).

Safety for use in pregnancy has not been established. Women of childbearing age should be advised to avoid pregnancy during fluorouracil therapy. Fluorouracil should only be used in women of childbearing 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 on the fetus.

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

† *Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal 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. To avoid possible harmful effects in the infant, breast-feeding is not advised during fluorouracil therapy.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable 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 section 4.4 Special warnings and precautions for use). 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. Other reported gastrointestinal symptoms are diarrhoea, stomatitis, proctitis, melaena, gastrointestinal haemorrhage, gastrointestinal ulcer 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) (see section 4.4 Special warnings and precautions for use).

Metabolism and nutrition disorders: Dehydration, decreased appetite, tumour lysis syndrome.

Immune system disorders: Anaphylactic reaction, hypersensitivity.

Dermatological: Alopecia[a] may be seen in a substantial number of cases, but is reversible. Nail disorders[b], dermatitis[c], cutaneous lupus erythematosus and hyperpigmentation of the nail beds and other body areas[d] have been reported. Skin rashes and fissures have been associated with fluorouracil therapy. Palmar-plantar erythrodysesthesia syndrome[e], thrombophlebitis and asymptomatic hyperpigmentation over vascular channels have also been reported. Continuous-infusion fluorouracil may increase incidence and severity of palmar-plantar erythrodysesthesia. Photosensitivity reaction.

Haematological: Leucopenia, primarily granulocytopenia commonly occurs. The nadir for white blood cell count usually occurs from the 9th to the 14th day after initiation of therapy, but

may occur as late as the 25th day. The count usually returns to normal by the 30th day. Thrombocytopenia may also occur, with the lowest platelet counts occurring from the 7th to the 17th day of therapy. Bone marrow failure and pancytopenia may also occur.

Cardiovascular: There have been reports of chest pain, tachycardia[f], breathlessness, arrhythmia[f], ECG changes (ST segment changes), angina pectoris[f,g], myocardial ischaemia[f], myocardial infarction[f], cardiac shock[f], cardiac failure[f], myocarditis[f], cardiomyopathy[f], pericarditis[f], stress cardiomyopathy[f], thrombophlebitis and haemorrhage after administration of fluorouracil. There have been reports of sudden death in patients readministered fluorouracil after a documented cardiovascular reaction.

Ocular: 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: Combination therapy with 5-fluorouracil and levamisole has been associated with leukoencephalopathy[h] and multifocal inflammatory leukoencephalopathy (MILE) (see section 4.4 Special warnings and precautions for use).

Neurotoxicity[h]: 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.

Infections and Infestations: Septic shock, sepsis, neutropenic sepsis, progressive multifocal leukoencephalopathy, 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. Pyrexia and chest pain.

a Reversible
b Such as partial or complete detachment of nails
c Manifests often as itchy maculopapular rash on the extremities
d Skin hyperpigmentation also refers to asymptomatic hyperpigmentation over vascular channels
e Observed in patients who received 5-fluorouracil and leucovorin bolus administration
f Listed cardiac disorders associated with 5-fluorouracil, may lead to cardiac arrest
g Observed in patients receiving high dose leucovorin and 5-fluorouracil bolus and continuous infusion
h Symptoms may persist after therapy is discontinued.

4.9 Overdose

Signs and symptoms

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 manifestations would be nausea, vomiting, diarrhoea, gastrointestinal ulcers and haemorrhage and myelosuppression (include thrombocytopenia, leucopenia and granulocytopenia).

Treatment

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. Patients who have been exposed to an overdose of fluorouracil should be monitored haematologically for at least 4 weeks. Should abnormalities appear, appropriate therapy should be utilised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

After intravenous administration, fluorouracil is distributed through the body water. The plasma half-life is 8 to 22 minutes and is dose dependent. Fluorouracil disappears from the blood within 4 hours. It is preferentially taken up by actively dividing tissues and 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.

5.3 Preclinical safety data

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.*

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

Water for injections

6.2 Incompatibilities

Admixture with acidic drugs or drugs that decompose in an alkaline environment should be avoided. Fluorouracil is reported to be incompatible with cytarabine, diazepam, methotrexate, platinum compounds, doxorubicin (and presumably other anthracyclines that are unstable at alkaline pH), and calcium folinate (leucovorin) or levoleucovorin calcium.

6.3 Shelf life

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

6.4 Special precautions for storage

Store at 8 - 25°C. Do not refrigerate. Protect from light.

6.5 Nature and contents of container

DBL Fluorouracil Injection BP is available in clear glass vials containing 25 mg/mL or 50 mg/mL of fluorouracil in the following presentations and pack sizes.

2.5 g/100 mL	Glass Type I Clear	1 vial 10 vials
500 mg/10 mL	Glass Type I Clear	1 vial (Onco-vial) with adapter 5 vials
1 g/20 mL	Glass Type I Clear	5 vials
2.5 g/50 mL	Glass Type I Clear	1 vial

Not all presentations may be available locally.

6.6 Special precautions for disposal

Handling precautions

As with all antineoplastic agents, trained personnel should prepare DBL Fluorouracil Injection BP. This should be performed in a designated area, preferably a cytotoxic laminar flow cabinet

with table surfaces protected with disposable plastic-backed absorbent paper, should be designated for the handling of the drug. 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 and a physician contacted. If the drug is ingested or inhaled inadvertently, immediate medical attention should be sought. 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 DBL Fluorouracil Injection BP, or articles associated with body waste should be disposed of by placing in a double sealed polythene bag and incinerated at 1100°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 5% sodium hypochlorite. 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 labelled ‘CYTOTOXIC WASTE FOR INCINERATION AT 1100°C’. Waste material should be incinerated at 1100°C for at least 1 second. Clean the remaining spill area with copious amounts of water.

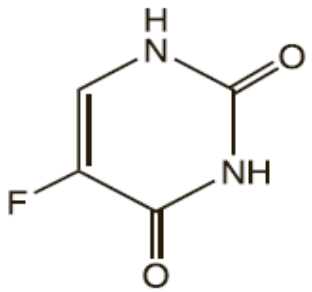
Single use only. Discard unused portion.

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.

6.7 Physicochemical properties

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.

Chemical Structure



Molecular formula: $C_4H_3FN_2O_2$

Molecular weight: 130.1

CAS Number

51-21-8

7. MANUFACTURER

Hospira Australia Pty Ltd
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Mulgrave, Victoria 3170
Australia

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