

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Fluorouracil 25 mg/ml Solution for injection.

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of DBL™ Fluorouracil containing 25 mg or 50 mg of fluorouracil. DBL™ Fluorouracil is a sterile preservative free solution of 5-Fluorouracil in Water for Injection, prepared with the aid of Sodium Hydroxide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

DBL™ Fluorouracil Injection BP is a clear, colourless to slightly yellow solution.

The pH of the solution is approximately 8.9.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL™ Fluorouracil Injection 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

Dose

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.

The total daily dose of fluorouracil should not exceed 1 gram. 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 (W.B.C. count less than 5,000 per mm³; platelet count less than 100,000 per mm³).
4. impaired hepatic and/or renal function.

The following regimes 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 300-500mL of 5% glucose given over a period of 4 hours. The infusion may be repeated daily until the first gastrointestinal side effects appear (stomatitis, diarrhoea, leucopenia, thrombocytopenia).

Treatment must be discontinued until the side effects have receded (until the W.B.C. count has risen to 3,000 - 4,000 per mm³ and the platelet count to 80,000 - 100,000 per mm³). The patient may then be placed on a maintenance therapy programme.

Intravenous Injection:

12 mg/kg bodyweight daily for 3 consecutive days.

Providing there are no signs of toxic effects, the patient may then be given 6mg/kg I.V. on the 5th, 7th and 9th days.

If after the 9th day there is still no sign of toxicity, the patient may be placed on maintenance therapy. In all instances toxic side effects must disappear before maintenance therapy is started.

Maintenance Therapy:

5 - 10 mg/kg bodyweight by I.V. injection once a week. Toxic symptoms seldom occur during maintenance therapy. If, however, they do appear, therapy must be discontinued until the symptoms regress.

Methods of Administration

DBLTM Fluorouracil Injection may be administered by intravenous infusion or intravenous injection.

Fluorouracil may be used in combination with other cytostatic agents or radiotherapy. In such cases doses should be correspondingly reduced. DBLTM Fluorouracil Injection may also be administered as a 24 hour intra-arterial continuous drip infusion (5 - 7. mg/kg bodyweight daily).

4.3 Contraindications

Fluorouracil is contraindicated in patients who are debilitated, who are suffering from bone marrow depression following radiotherapy or therapy with other antineoplastic agents, potential serious infection, poor nutritional state and in patients who are pregnant.

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).

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 re-administered after a documented cardiovascular reaction (arrhythmia, angina, ST segment changes) as there is a risk of sudden death.

Any form of therapy which adds to the stress of the patient, interferes with nutritional uptake or depresses bone marrow function, will increase the toxicity of fluorouracil.

Adequate treatment with fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C.) 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. Daily monitoring of platelets and W.B.C. counts are recommended and treatment should be stopped if platelets fall below 100,000 per mm³ or the W.B.C. count falls below 3,500 per mm³. If the W.B.C. count falls below 2,000 per mm³, it is recommended that the patient be placed in protective isolation in the hospital and given the appropriate preventative treatment for systemic infection.

Treatment should also be discontinued at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhoea or bleeding from the G.I. tract.

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).

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, melena haemorrhage, oral ulceration, evidence of gastrointestinal ulceration or bleeding. 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.

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

There is an increased risk of death associated with re-administration of fluorouracil in patients with a documented cardiovascular reaction (See section 4.8).

Angina, ECG abnormalities and myocardial infarction have been reported after administration of fluorouracil. Attention should therefore be paid to patients who experience chest pain during treatment, and patients with a history of heart disease.

Gastrointestinal effects

Loss of appetite, nausea and vomiting are common adverse effects, which generally occur during the first week of therapy. These adverse effects can often be alleviated by antiemetics, and generally subside within 2 to 3 days. Stomatitis is one of the most common and often the earliest sign of specific toxicity, appearing as early as the fourth day, but more commonly on the fifth to eighth day of therapy. Diarrhea is also a common adverse effect. It is usually mild and usually occurs later in treatment. Severe diarrhea may also be accompanied by dehydration and melena.

Renal and hepatic impairment

Fluorouracil should be used with caution in patients with renal and/or hepatic dysfunction.

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.

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. 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.

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).

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.

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.

Use in elderly

Fluorouracil should be used with caution in elderly patients. Aged 70 years or older and the female gender are reported independent risk factors for severe toxicity from fluorouracil based chemotherapy. Close monitoring for multiple organ toxicities and vigorous supportive care of those with toxicity are necessary.

4.5 Interaction with other medicines and other forms of interaction

Cytotoxic agents: All myelosuppressive drugs (e.g., Cytotoxic agents used in combination chemotherapy) can increase hematotoxicity 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 drugs include methotrexate, metronidazole, 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.

Pretreatment with cimetidine prior to IV fluorouracil increased the AUC by 27%. The total body clearance was reduced by 28% and may increase plasma fluorouracil concentrations. This effect is probably due to both inhibition of hepatic enzymes and reduction of hepatic blood flow. Caution should be taken if the patient receives fluorouracil and cimetidine concurrently.

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 levels (see section 4.4).

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). In the case of accidental administration of nucleoside analogues that inhibit DPD activity to patients treated with fluorouracil, effective measures should be taken to reduce fluorouracil toxicity. Immediate hospitalization is recommended.

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 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.

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

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.

Pregnancy - Category D

This category specifies drugs which have caused an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

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

Fluorouracil is therefore strictly contraindicated in pregnancy.

Breast-feeding

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 effect of fluorouracil on the ability to drive and use machinery has not been systematically evaluated.

4.8 Undesirable 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.

Infections and Infestations

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

Blood and lymphatic system disorders

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.

Nervous system disorders

Neurological: Combination therapy with 5-fluorouracil and levamisole has been associated with leukoencephalopathy and 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.

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

Eye disorders

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.

Cardiac disorders

There have been reports of myocardial infarction*, angina pectoris*, cardiac shock*, cardiac failure*, cardiomyopathy*, myocarditis*, pericarditis*, chest pain, tachycardia, breathlessness, arrhythmia and E.C.G. changes (ST segment changes) after administration of fluorouracil. There have been reports of sudden death in patients readministered fluorouracil after a documented cardiovascular reaction.

Gastrointestinal disorders

The most pronounced dose-limiting toxic effects of fluorouracil are on the normal, rapidly proliferating tissues of the bone marrow and the lining of the gastrointestinal tract. Diarrhoea, nausea and vomiting are seen commonly during therapy and may be treated symptomatically. Nausea and vomiting may be controlled with an appropriate antiemetic. Other reported gastrointestinal symptoms are diarrhoea, proctitis, melaena and oesophagitis, Gastrointestinal haemorrhage, Gastrointestinal ulcer, 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).

Skin and subcutaneous tissue disorders

Alopecia may be seen in a substantial number of cases, but is reversible. Dermatitis, hyperpigmentation, changes in the nail beds and ataxia have been reported. Skin rashes and fissures 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 reaction.

Other

Local injection site reaction. Fevers have also been reported. Rarely, anaphylaxis or generalised allergic reactions have occurred in patients receiving fluorouracil. Pyrexia and chest pain. Haemorrhage and thrombophlebitis have occurred.

* Listed cardiac disorders associated with 5-fluorouracil, may lead to cardiac arrest.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

The possibility of overdosage with fluorouracil is unlikely in view of the mode of administration.

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 hemorrhage 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Fluorouracil is an analogue of uracil, a component of ribonucleic acid. The drug is believed to function as an antimetabolite. After intracellular 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.

5.2 Pharmacokinetic properties

After intravenous administration, fluorouracil is distributed through the body water and disappear 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 C.S.F

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

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*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide

Water for injection

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

24 months

18 months (only for 250 mg/5 mL)

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.

Strength	Packs
500 mg/20 mL	10 x 20mL vials
250 mg/5 mL	5 x 5mL vials
2.5 g/100 mL	1 x 100mL vial
500 mg/10 mL	5 x 10mL vials
1 g/20 mL	5 x 20mL vials
2.5 g/50 mL	1 x 50mL vial
250 mg/10 mL	5 x 10 mL vials

6.6 Special precautions for disposal and other handling

Spill 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.

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

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

Single use only. Discard unused portion.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Pfizer New Zealand Limited,

PO Box 3998

Auckland, New Zealand, 1140

Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

27 August 1986

10. DATE OF REVISION OF THE TEXT

13 July 2020

Summary table of changes

Section	Summary of new information
Throughout	Minor editorial changes made through out to align datasheet guidance
4.3	Contraindications updated to include: poor nutritional state and potential serious infection
4.4	Addition of precaution relating to Gastrointestinal effects
4.5	Addition of interactions with the following: Cimetidine Metronidazole
4.6	<ul style="list-style-type: none">• Addition of warning statement in pregnancy
4.8	Update Adverse events including: Blood and lymphatic disorders, Vascular disorders, gastrointestinal disorders, skin disorders