Summary of Product Characteristics

1. Name of the Medical Product

Drug Product	**:**	Fluorouracil Injection USP (500 mg / 10 mL)
Generic Name	**:**	Fluorouracil Injection USP
Strength	**:**	Each mL of sterile preservative and pyrogen free aqueous clear and colourless solution containing 50 mg of Fluorouracil USP in 1.0 mL of Water for Injection USP.

2. Quality and Quantitative Composition

Composition

Each mL contains:

Fluorouracil USP	50 mg
Water for injection USP	q.s. to 1 mL

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Sterile preservative and pyrogen free aqueous clear and colourless solution for Intravenous Infusion as parenteral preparation

4. Clinical Particulars

4.1 Therapeutic Indications

Fluorouracil may be used alone, or in combination forits palliative action in the management of common malignancies particularly cancer of the colon and breast, either as a single agent or in combination with other cytotoxic agents.

4.2 Posology and method of administration

Selection of an appropriate dose and treatment regime will depend upon the condition of the patient, the type of carcinoma being treated and whether Fluorouracil is to be administered alone or in combination with other therapy. Initial treatment should be given in hospital and the total daily dose should not exceed 1 gram. It is customary to calculate the dose in accordance with patient's actual weight unless there is obesity, oedema or some other form of abnormal fluid retention such as ascites. In this case, ideal

weight should be used as the basis for the calculation. Reduction of the dose is advisable in patients with any of the following:

1) Cachexia

2) Major surgery within preceding 30 days

3) Reduced bone marrow function

4) Impaired hepatic or renal function

Fluorouracil injection can be given by intravenous injection or, intravenous or intra-arterial infusion. Fluorouracil injection should not be mixed directly, in the same container, with other chemotherapeutic agents or intravenous additives.

Adult Dose

The following regimen has been recommended for use as a single agent:

Initial Treatment: This may be in the form of an infusion or an injection, the

Intravenous infusion: 15mg/kg bodyweight but not more than 1g per infusion, diluted in 500ml of 5% glucose or 0.9% NaCl injection and given by intravenous infusion at a rate of 40 drops per minute over 4 hours. Alternatively the daily dose may be infused over 30 - 60 minutes or may be given as a continuous infusion over 24 hours. The infusion may be repeated daily until there is evidence of toxicity or a total dose of 12 - 15g has been reached.

Intravenous Injection: 12mg/kg bodyweight, but not more than the recommended 1g daily dose may be given daily for 3 days and then, if there is no evidence of toxicity, 6mg/kg on alternate days for 3 further doses. An alternative regimen is 15mg/kg as a single intravenous injection once a weekthroughout the course.

Intra-arterial Infusion: 5/7.5mg/kg may be given by 24 hour continuous intra-arterial infusion.

Maintenance Therapy: An initial intensive course may be followed by maintenance therapy providing there are no significant toxic effects. In all instances, toxic side effects must disappear before maintenance therapy is started. If toxic symptoms appear during maintenance, therapy must be discontinued until the symptoms resolve.

The initial course of fluorouracil can be repeated after an interval of 4 to 6 weeks from the last dose or, alternatively, treatment can be continued with intravenous injections of 5-15mg/kg bodyweight at weekly intervals.

This sequence constitutes a course of therapy. Some patients have received up to 30g at a maximum rate of 1 g daily. A more recent alternative method is to give 15mg/kg IV once a week throughout the course of treatment. This obviates the need for an initial period of daily administration.

In combination with Irradiation: Irradiation combined with 5FU has been found to be useful in the treatment of certain types of metastatic lesions in the lungs and for the relief of pain caused by recurrent, inoperable growth. The standard dose of 5FU should be used.

Children: No recommendations are made regarding the use of Fluorouracil in children.

Elderly: Fluorouracil should be used in the elderly with similar considerations as in younger adult dosages, notwithstanding that incidence of concomitant medical illness is higher in the former group.

Routes of administration:

Fluorouracil Injection can be given by intravenous injection or intravenous or intra-arterial infusion.

4.3 Contraindications

Fluorouracil is contraindicated in patients who have any known hypersensitivity to fluorouracil, are seriously debilitated or are suffering from bone marrow depression after radiotherapy or treatment with other antineoplastic agents, or who are suffering from a potentially serious infection.

Fluorouracil is strictly contraindicated in pregnant or breast feeding women.

Flourouracil should not be used in the management of non-malignant disease.

4.4 Special Warnings and precautions for use

WarningsIt is recommended that Fluorouracil be given only by, or under the strict supervision of a qualified physician who is conversant with the use of potent antimetabolites.

All patients should be admitted to hospital for initial treatment.

Fluorouracil is contraindicated in patients who have a poor nutritional state.

Adequate treatment with Fluorouracil is usually followed by leucopenia, the lowest white blood cell (W.B.C) count commonly being observed between the 7th 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 platelet and W.B.C count is 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 total count is less than 2000mm3, and especially if there is granulocytopenia, it is recommended that the patient be placed in protective isolation in the hospital and treated with appropriate measures to prevent systemic infection.

Treatment should be stopped at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhoea, bleeding from the gastrointestinal tract of haemorrhage at any site, oesophagopharyngitis or intractable vomiting. Fluorouracil should be resumed only when the patient has recovered from the above signs. 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.

Fluorouracil should be used with extreme caution in poor risk patients who have recently undergone surgery, have a history of high-dose irradiation of bone marrow-bearing areas (pelvis, spine, ribs, etc.) or prior use of another chemotherapeutic agent causing myelosuppression, have a widespread involvement of bone marrow by metastatic tumours, or those with reduced renal or liver function, jaundice or who have a poor nutritional state. Fluorouracil should also be used with caution in patients with heart disease. Isolated cases of angina, ECG abnormalities and rarely, myocardial infarction have been reported following administration of Fluorouracil. Care should be therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with a history of heart disease. Careful consideration should be given to re-administration of Fluorouracil after a documented cardiovascular reaction (arrhythmia, angina, ST segment changes) as there is a risk of sudden death. Severe toxicity and fatalities are more likely in poor risk patients, but have occasionally occurred in patients who are in relatively good condition. Any form of therapy which adds to the stress of the patient, interferes with nutritional uptake or depresses the bone marrow function, will increase the toxicity of fluorouracil. If therapy is continued careful monitoring of thepatient is required.

Rarely, severe and unexpected toxic reactions (including stomatitis, diarrhoea, neutropenia and neurotoxicity) have been reported in association with fluorouracil.

These reports of increased toxicity in patients who have reduced activity/deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD), which appears to cause prolonged clearance of fluorouracil.
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. The immunosuppressive effect of fluorouracil may cause a higher incidence of microbial infections, delayed wound healing and bleeding of the gums.

Nucleoside analogues, e.g. Brivudin and sorivudin, which affect DPD activity may cause increased plasma concentrations and increased toxicity of fluoropyrimidines. Therefore, an interval of at least 4 weeks between administration of fluorouracil and brivudin, sorivudin or analogues should be kept. In the case of accidental administration of nucleoside analogues to patients treated with fluorouracil, effective measures should be taken to reduce fluorouracil toxicity. Immediate hospitalisation is recommended. Any measure to prevent systemic infections and dehydration should be commenced.

4.5 Interaction with other medicinal products and other form of interactions

Various purines, pyrimidines, and antimetabolites have shown biochemical modulation offluorouracil in in vitro test systems. Purines include inosine, guanosine, guanosine-5'-phosphate and deoxyinosine. Pyrimidines include thymidine, uridine and cytidine. Antimetabolites include methotrexate, tamoxifen, interferon, phosphonoacteyl-L-aspartate (PALA), allopurinol, hydroxyurea, dipyridamol and leucovorin (folinic acid). Synergistic cytotoxic interactions, such as those involving fluorouracil with leucovorin, have shown beneficial therapeutic effects, particularly in colon cancer. However, the drug combination may result in increased clinical toxicity (gastrointestinal side effects).

of the fluorouracil component. Other drugs include metronidazole and 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.

Marked elevations of prothrombin time and INR have been reported in a few patients stabilised on warfarin therapy following initiation of fluorouracil regimes.

A clinically significant interaction between the antiviral sorivudine and fluorouracil prodrugs, resulting from inhibition of dihydropyrimidine dehydrogenase by sorivudine or chemically related analogues. Caution should be taken when using fluorouracil in conjunction with medications which may affect dihydropyrimidine dehydrogenase activity.

Combination therapy with 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 fluorouracil and levamisole are discontinued, and corticosteroids given. The use of levamisole and 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
leucovorin. 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. Vaccination with a live vaccine should be avoided in patients receiving 5-fluorouracil due to the potential for serious or fatal infections. Contact should be avoided with people who have recently been treated with polio virus vaccine.

Patients with leukaemia who are in remission should not receive vaccines containing weakened viruses until three months has elapsed since their last chemotherapy session.

Furthermore, immunisation with orally administered vaccines containing the poliomyelitis virus must be postponed for those persons coming into direct contact with the patient, particularly family members.

4.6 Pregnancy and lactation

Fluorouracil is strictly contraindicated in pregnant and breast-feeding women.

Women of childbearing potential should be advised to avoid becoming pregnant and use an effective method of contraception during treatment with Fluorouracil and up to 6 months afterwards. If the drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be fully informed of the potential hazard to the foetus and genetic counselling is recommended. Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

There are no adequate and well-controlled studies in pregnant women, however, fatal defects and miscarriages have been reported.

Men treated with Fluorouracil are advised not to father a child during and for up to 6 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Fluorouracil.

Since it is not known whether Fluorouracil passes into breast milk, breast-feeding must be discontinued if the mother is treated with Fluorouracil.

4.7 Effects on ability to drive and use machine

No studies on the effects on the ability to drive and use machinery have been performed.

Fluorouracil may induce side effects such as nausea and vomiting. It can also produce adverse events of the nervous system and visual changes which could interfere with driving or the usage of heavy machinery.

4.8 Undesirable effects

Frequencies are defined using the following convention:

Very common (≥1/10),

Common (≥ 1/100 to < 1/10),

Uncommon (≥ 1/1000 to < 1/100),

Rare (≥ 1/10000 to < 1/1000),

Very rare (< 1/10000),

Not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:

Very common: Myelosuppression (leucopenia, pancytopenia and thrombocytopenia);

agranulocytosis, anaemia

Immune system disorders:

Rare: Hypersensitivity reactions, generalised anaphylactic and allergic reactions.

Psychiatric disorders:

Uncommon: Euphoria.

Rare: a reversible confusional state may occur.

Very rare: Disorientation.

Eye disorders:

Systemic fluorouracil treatment has been associated with various types of ocular toxicity.

Uncommon: Incidences of excessive lacrimation, dacryostenosis, visual changes and photophobia.

Vascular disorders:

Rare: Cerebral, intestinal and peripheral ischemia, Raynaud's syndrome, thromboembolism,

Thrombophlebitis

Uncommon: Hypotension

Gastrointestinal disorders:

Very common: Diarrhoea, nausea and vomiting are observed quite commonly during therapy and may be treated symptomatically. An anti-emetic may be given for nausea and vomiting. Additionally,events of anorexia, stomatitis (symptoms include soreness, erythema or ulceration of the oral cavity or dysphagia); proctitis, oesophagitis.

Uncommon: gastrointestinal ulcerations and bleeding (may result in therapy being discontinued).

Skin and subcutaneous tissue disorders:

Very common: Alopecia may be seen in a substantial number of cases, particularly females, but is reversible.

Palmar-plantar erythrodysesthesia syndrome has been reported as an unusual complication ofhigh dose bolus or protracted continuous therapy for 5-fluorouracil. The syndrome begins with dysaesthesia of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot.

Uncommon: Other side effects include dermatitis, pigmentation, changes in nails, (e.g. diffuse superficial blue pigmentation, hyperpigmentation, nail dystrophy, pain and thickening of the nail bed, paronychia) dry skin, fissure erosion, erythema, pruritic maculopapular rash, exanthema, photosensitivity, hyperpigmentation of the skin, streaky hyperpigmentation or depigmentation near the veins.

General disorders and administration site conditions:

Very common: Malaise, weakness

Not known: Fever, vein discolouration proximal to injection sites

Cardiac disorders:

Very common: ECG changes

Common: angina pectoris-like chest pain

Uncommon: arrhythmia, myocardial infarction, myocardial ishchaemia dilative cardiomyopathy

Very rare: Cardiac arrest and sudden cardiac death.

Special attention is advisable in treating patients with a history of heart disease or those who develop chest pain during treatment.

Nervous system disorders:

Uncommon:Nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramidal signs, and somnolence.

Very rare: Cases of leucoencephalopathy have also been reported. With symptoms including ataxia, acute cerebellar syndrome, dysarthria, myasthenia, aphasia, convulsion or coma in patients receiving high doses of 5-fluorouracil and in patients with dihydropyrimidine dehydrogenase deficiency, kidney failure.

Not known: Peripheral neuropathy may occur.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Over dosage

The symptoms and signs of overdosage are qualitatively similar to the adverse reactions and should be managed as indicated under "Special Warnings and Precautions" and "Undesirable Effects".

Patients in which an overdose of fluorouracil is detected should be closely monitored for at least 4 weeks.

5. Pharmacological p roperties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Antineoplastic agents; Antimetabolites; Pyrimidine analogues

ATC code:

L01BC02
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. Flourouracil may also interfere with RNA synthesis.

5.2 Pharmacokinetics Properties

After intravenous administration, Flourouracil is distributed through the body water and disappears from the blood within 3 hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil ready enters the C.S.F and brain tissue.

Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose dependant. Following a single intravenous dose of Fluorouracil approximately 15% of the dose is excreted unchanged in the urine within 6 hours; over 90% of this is excreted in the first hour. The remainder is mostly metabolised in the liver by the usual body mechanisms for uracil.

5.3 Preclinical safety data

Preclinical information has not been included because the toxicity profile of fluorouracil has been established after many years of clinical use.

6. Pharmaceutical Particulars

6.1 List of excipients

Tromethamine (Tis buffer)

Sodium Hydroxide

Water for Injection

6.2 Incompatibilities

Fluorouracil is incompatible with Carboplatin, Cisplatin, Cytarabine, Diazepam, Doxorubicin, other Anthracyclines and possibly Methotrexate.

Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided.

6.3 Shelf life

24 months from the date of manufacturing, when retained in the original carton.

Proposed Shelf Life (After first opening containers)

As the finished product is sterile formulation, from the microbiological point of view, the product should be used immediately, but after further dilution is should not longer than 24 hours at 2º to 8ºC.

Proposed Storage Conditions

Unopened vials of Fluorouracil Injection USP is stable until the expiration date indicated on the package when stored at controlled room temperature, and protected from direct exposure to light i.e at a temperature not exceeding 25°C (77°F) and that allows for excursions between 15° and 30°C (59° and 86°F).

6.4 Special precautions for storage

Store at 20º to 25º (68º to 77º F), excursion are permitted from 15º to 30º (59º to 86º F). Protect from light. Do not freeze.

6.5 Special precautions for disposal and other handlings

Should be administered only by or under the direct supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents.

Contamination

Fluorouracil Injection should only be prepared for administration by professionals who have been trained in the safe use of the preparation. Preparation should only be carried out in an aseptic cabinet or suite dedicated for the assembly of cytotoxics.

In the event of spillage, operators should put on gloves, face mask, eye protection and disposable apron and mop up the spilled material with a absorbent material kept in the area for that purpose. The area should then be cleaned and all contaminated material transferred to a cytotoxic spillage bag or bin and sealed for incineration.

Contamination

Fluorouracil is an irritant, contact with skin and mucous membranes should be avoided.

In the event of contact with the skin or eyes, the affected area should be washed with copious amounts of water or normal saline.

A bland cream may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected or if the preparation is inhaled or ingested.

Preparation Guidelines

a) Chemotherapeutic agents should be prepared for administration only by professionals who have been trained in the safe use of the preparation.

b) Operations such as reconstitution of powder and transfer to syringes should be carried out only under aseptic conditions in a suite or cabinet dedicated for the assembly of cytotoxics.

c) The personnel carrying out these procedures should be adequately protected with clothing, gloves and eye shield.

d) Pregnant personnel are advised not to handle chemotherapeutic agents.

Disposal

Syringes and adaptors containing remaining solution, absorbent materials, and any othercontaminated material should be placed in a thick plastic bag or other impervious container and incinerated at 700°C.

Dilution

Fluorouracil Injection may be diluted with Glucose 5% Injection or Sodium Chloride 0.9% Injection or Water for Injections immediately before parenteral use.

6.5. Nature and contents of container

20 mL Amber Glass Vial USP Type I

20 mm Bromo butyl rubber plug

20 mm Aluminium flips off seal

7. Marketing authorisation holder

Beta Drugs Limited
Kharuni-Lodhimajra Road,
Vill: Nandpur, Baddi, Distt. Solan,

Himachal Pradesh, 173205 INDIA

8. Marketing authorisation number(s)

08160/08168/NMR/2020

9. Date of first authorisation

29 Nov 2022

10. Date of revision of the text

July 2024