

PRODUCT NAME: FLUOROURACIL INJECTION BP 50MG/ ML

Summary Of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Fluorouracil Injection BP 50mg/ Ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Fluorouracil Injection contains:

250 mg Fluorouracil in 5 ml solution (50 mg/ml)

500 mg Fluorouracil in 10 ml solution (50 mg/ml)

1000 mg Fluorouracil in 20 ml solution (50 mg/ml)

2500 mg Fluorouracil in 50 ml solution (50 mg/ml)

5000 mg Fluorouracil in 100 ml solution (50 mg/ml)

For excipients see section 6.1

3. PHARMACEUTICAL FORM

Sterile solution for injection.

Clear, pale yellow, sterile solution, free from preservative and visible particulate.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluorouracil may be used alone, or in combination for its 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

Routes of administration:

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

Selection of an appropriate dose and treatment regimen 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 the 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:

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4. CLINICAL PARTICULARS CONT/D.

4.2 Posology and method of administration cont/d.

- 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.

Adult dose: The following regimes have been recommended for the use as a single agent:
Initial treatment: This may be in the form of an infusion or an injection, the former usually being preferred because of lesser toxicity.

Intravenous infusion: 15 mg/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 12-15 g has been reached.

Intravenous injection: 12mg/ kg bodyweight 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 regime is 15mg/kg as a single intravenous injection once a week throughout the course.

Intra- arterial infusion: 5-7.5 mg/ 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.

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 injection of 5-15 mg/kg at weekly intervals.

This sequence constitutes a course of therapy. Some patients have received up to 30g at a maximum rate of 1g daily. A more recent alternative method is to give 15 mg/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 5-FU 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 5-FU 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 with normal adults' dosages.

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4. CLINICAL PARTICULARS CONT/D.

4.3 Contra-indications

Fluorouracil is contra-indicated in seriously debilitated patients or those with bone marrow depression after radiotherapy or treatment with other antineoplastic agents. Fluorouracil is strictly contra-indicated in pregnant or breast feeding woman. Fluorouracil should not be used in the management of non-malignant disease.

4.4 Special Warnings and special precautions for use

It 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. 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 2000 mm³, 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 also 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 G.I tract or haemorrhage at any site. 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 caution in patients with reduced renal or liver function or jaundice. Isolated cases of angina, ECG abnormalities and rarely, myocardial infraction have been reported following administration of Fluorouracil. Care should therefore be exercised in treating patients who experience chest pain during courses of treatment, or patients with history of heart disease.

4.5 Interaction with other medicinal products and other forms of interactions

Drug interactions: Various agents have been reported to biochemically modulate the antitumour efficacy or toxicity of Fluorouracil, common drugs include Methotrexate, Metronidazole, Leucovorin as well as Allopurinol and Cimetidine which can affect the availability of the active drug.

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4. CLINICAL PARTICULARS CONT/D.

4.6 Pregnancy and lactation

Fluorouracil is strictly contraindicated in pregnant and breast feeding woman.

4.7 Effects on ability to drive and use machines

Not known.

4.8 Undesirable effects

Undesirable effects: 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.

Alopecia may be seen in a substantial number of cases, particularly females, but is reversible. Other side effects include dermatitis, pigmentation, changes in the nails, ataxia and fever.

There have been reports of chest pain, tachycardia, breathlessness and E.C.G changes after administration of Fluorouracil. Special attention is advisable in treating patients with a history of heart disease or those who develop chest pain during treatment.

Leucopenia is common and the precautions described above should be followed.

Systemic Fluorouracil treatment has been associated with various types of ocular toxicity. A transient reversible cerebellar syndrome can occur after the use of 5- Fluorouracil. Rarely, a reversible confusional state may occur. Both neurological conditions usually respond to withdrawal of 5- Fluorouracil.

Additionally several other reports have been noted including:

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

Palmar- Plantar Erythrodysesthesia Syndrome has been reported as an unusual complication of high dose bolus or protracted continuous therapy with Fluorouracil.

Thrombophlebitis/ Vein tracking.

4.9 Overdose

The symptoms and signs of overdosage are qualitatively similar to the adverse reactions and should be managed as indicated under “Undesirable effects” and “Special warnings and precautions for use”.

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimetabolite

ATC code: L01B C02

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 disappears from the blood within 3 hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil readily enters the CSF and brain tissue.

Following IV administration, the plasma elimination half-life averages about 16 minutes and is dose dependent. Following a single IV 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

No relevant information additional to that included elsewhere in the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Hydroxide; Water for injections.

6.2 Incompatibilities

Fluorouracil is incompatible with Carboplatin, Cisplatin, Diazepam, Doxorubicin, other Anthracyclines and possibly Methotrexate. Formulated solutions are alkaline and it is recommended that a mixture with acidic drugs or preparations should be avoided.

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Summary Of Product Characteristics

6. PHARMACEUTICAL PARTICULARS Cont/d

6.3 Shelf life

24 months

Chemical and physical in-use stability has been demonstrated for 24hours at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24hours at 2-8°C unless reconstitution/ dilution (etc) has taken place in controlled and validated aseptic conditions

6.4 Special precautions for storage

Do not store above 25°C. Keep container in the outer carton to protect from light. Do not refrigerate. Unused portions of opened vials or prepared infusions if not used immediately must be stored at 2-8°C for no longer than 24 hours from the time of opening or preparation.

The product should be discarded if it appears brown or dark yellow in solution.

6.5 Nature and contents of container

Fluorouracil Injection BP 50mg/ ml is available in: 5ml, 10ml, 20ml, 50ml and 100ml glass vials in packs of five vials.

Glass vial with a bromobutyl stopper and aluminium cap with a plastic top.
Each vial contains a sterile solution for injection.

6.6 Special precautions for disposal

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

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 a designated area.

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.

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6. Pharmaceutical particulars Cont/d

6.6 Special precautions for disposal cont/d.

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 in the designated area.
- c. The personnel carrying out these procedures should be adequately protected with clothing, gloves and eyeshield.
- d. Pregnant personnel are advised not to handle chemotherapeutic agents.

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

Diluents: Fluorouracil Injection BP may be diluted with Glucose or Sodium Chloride Injection BP or Water for injections BP immediately before parenteral use.

7. MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Ltd
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Croydon
CR0 0XT
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8. MARKETING AUTHORISATION NUMBER(S)

PL 12762/ 0091

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

4 August 2003

10. DATE OF REVISION OF THE TEXT

March 2007