Fluorouracil EbeweDatasheet

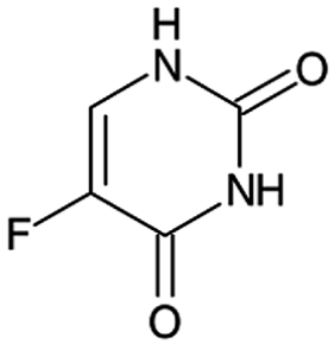
NAME OF THE MEDICINE

Fluorouracil injection

Composition

Active. Fluorouracil.

Inactive. Water for injections, sodium hydroxide.



Fluorouracil

DESCRIPTION

Chemical name: 5-fluoro-1H, 3H -pyrimidine-2, 4-dione. $C_4H_3FN_2O_2$. MW: 130.1. CAS: 51-21-8. Fluorouracil is a white to almost white, practically odourless, crystalline powder. It is sparingly soluble in water, slightly soluble in alcohol and practically insoluble in chloroform and ether. The pH of the fluorouracil injection solution is approximately 8.9.

PHARMACOLOGY

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

Pharmacokinetics. After intravenous administration, fluorouracil is distributed throughout body tissues and fluids. The plasma half-life is 8 to 22 minutes and is dose dependent. Fluorouracil disappears from the blood within four hours. It is preferentially taken up by actively dividing tissues and tumours after conversion to its nucleotide. Fluorouracil readily enters the cerebrospinal fluid (CSF).

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

INDICATIONS

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

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

CONTRAINDICATIONS

- Known hypersensitivity to fluorouracil.
- Poor nutritional state
- Depressed Bone marrow (leucocyte count less than 5,000/mm^3, platelet count less than 100,000/mm^3)
- potentially serious infection.
- pregnancy.

PRECAUTIONS

Fluorouracil should be administered only under the constant supervision by physicians experienced in therapy with cytotoxic agents and only when the potential benefits of fluorouracil outweigh the possible risks. Because of the possibility of severe toxic reactions,appropriate facilities should be available for adequate management of complications should they arise.

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.

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.

Cardiotoxicity

There is an increased risk of death associated with re-administration of fluorouracil in patients with a documented cardiovascular reaction to fluorouracil (see Adverse Effects).

Myelosuppression

Cytotoxic agents, including fluorouracil, may produce myelosuppression (including, but not limited to leucopenia, granulocytopenia, pancytopenia, and thrombocytopenia).Leucopenia and thrombocytopenia commonly follow treatment of fluorouracil. Daily monitoring of platelet and white blood cell counts is recommended. Treatment with fluorouracil should be discontinued if the leucocyte count falls rapidly or if it falls below 3,500/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.

Combination Chemotherapy/Radiotherapy

Extreme caution is necessary when administering fluorouracil to patients who have had high dose pelvic irradiation or have been previously treated with alkylating agents.Fluorouracil treatment may potentiate necrosis caused by radiation. Concomitant use of other chemotherapeutic agents may depress bone marrow function and increase the toxicity of fluorouracil.

Impaired Renal Function.

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

Impaired Hepatic Function.

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

Dihydropyrimidine dehydrogenase deficieny

Rarely, severe toxicity (e.g. stomatitis, diarrhoea, neutropenia, and neurotoxicity) associated with fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase (DPD) activity. Fatal outcome has been reported in some cases. Absence of this catabolic enzyme appears to result in prolonged clearance of fluorouracil. Special attention should be given to DPD status when evaluating patients experiencing fluorouracil– related toxicities.

Use in the Elderly.

Fluorouracil should be used with caution in elderly patients. An age of 70 years or older and the female gender are reported independent risk factors for severe toxicity from fluorouracil based chemotherapy. These effects may be additive in older women. While advanced age does not contradict this type of chemotherapy, close monitoring for multiple organ toxicities and vigorous supportive care for those with toxicity are required.

Carcinogenicity, Mutagenesis, Impairment of Fertility

Carcinogenicity: Long-term studies in animals to determine the carcinogenic potential of fluorouracil have not been performed. However there was no evidence of carcinogenicity in small groups of rats given fluorouracil orally at doses 0.01, 0.31 or 3 mg per rat 5 days per week for 52 weeks, followed by a 6 month observation period. On the basis of the available data, no evaluation can be made of the carcinogenic risk of fluorouracil to humans

Mutagenicity: Fluorouracil has been shown to be mutagenic and clastogenic in a number of studies. Oncogenic transformation of fibroblasts from mouse embryo has been induced *in vitro* by fluorouracil, but the relationship between oncogenicity and mutagenicity is not clear. A positive effect was observed in the micronucleus test on bone marrow cells of the mouse, and fluorouracil at very high concentrations produced chromosomal breaks in hamster fibroblasts *in vitro*.

Impairment of 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 125or 250mg/kg, administered intraperitoneally, have been shown to induce chromosomal aberrations and changes in chromosomal organisation of spermatogonia in rats. Spermatogonial differentiation was also inhibited by fluorouracil, resulting in transient infertility. However, in studies with a strain of mouse which is sensitive to the induction of sperm head abnormalities after exposure to a range of chemical mutagens and carcinogens, fluorouracil did not produce any abnormalities at oral doses of up to 80 mg/kg/day. In female rats, fluorouracil, administered intraperitoneally at weekly doses of 25 or 50 mg/kg for three weeks during the pre-ovulatory phase of oogenesis, significantly reduced the incidence of fertile matings, delayed the development of pre- and post-implantation embryos, increased the incidence of pre-implantation lethality and induced chromosomalanomalies 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 limited effect in producing zygote destruction. Compounds such as fluorouracil which interfere with DNA, RNA and protein synthesis might be expected to adversely affect gametogenesis. In general, use of a contraceptive is recommended during cytotoxic therapy.

Use in Pregnancy. (Category D)

Category D*. Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.*

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 whilst receiving the drug she should be advised of the potential hazards to the fetus.

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

Use in Lactation.

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

Interactionswith other medicines

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 medicinesinclude methotrexate, metronidazole and folinic acid (leucovorin).

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

Increased phenytoin plasma concentrations have been reported during concomitant use of phenytoin with capecitabine or its metabolite fluorouracil. Formal interaction studies between phenytoin and capecitabine have not been conducted, but the mechanism of interaction is presumed to be inhibition of CYP2C9 isoenzyme system by capecitabine. Serum levels of phenytoin sustained above the optional 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.

Compatibilities.

See Dosage and Administration, Compatibilities.

Incompatibilities

Admixtures with acidic medicines or medicines that are unstable in the presence of alkali should be avoided.

Immunosuppresant Effects/ Increased Susceptibility to Infections

Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents including fluorouracil, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving fluorouracil. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Effects on Laboratory Tests.

Fluorouracil could interfere with diagnostic tests of thyroid function by causing rises in total thyroxine and liothyronine due to increased globulin binding. Plasma albumin may be decreased because of drug-induced protein malabsorption

ADVERSE EFFECTS

The ratio between effective and toxic dose is small and therapy with fluorouracil is usually accompanied by some degree of adverse effects. Patients should be very carefully observed and dosage adjustment may have to be made. Deaths have been reported.

Gastrointestinal

The most pronounced and dose limiting toxic effects of fluorouracil are on the normal, rapidly proliferating cells of the bone marrow and the lining of the gastrointestinal tract.

Nausea and vomiting occur and may be treated symptomatically.

Stomatitis is usually an early sign of impending severe toxicity which may be evident after five to eight days of therapy. Symptoms include soreness, erythema or ulceration of the oral cavity or dysphagia. Other reported gastrointestinal symptoms are diarrhoea, proctitis and oesophagitis, therefore the dose may require adjustment or therapy may need to be

discontinued. Gastrointestinal side effects may be exacerbated if fluorouracil is given with folinic acid (leucovorin).

Dermatological.

Alopecia may be seen in a substantial number of cases, but it is reversible. Partial loss of nails, dermatitis and hyper- pigmentation of the nail beds and other body areas have been reported. Skin rashes have been associated with fluorouracil therapy.. Palmar plantar erythrodysaesthesia syndrome, thrombophlebitis and asymptomatic hyperpigmentation over vascular channels have also been reported. Continuous-infusion fluorouracil may increase incidence and severity of palmar-plantar erthrodysaesthesia, photosensitivity reactions.

Haematological.

Leucopenia, primarily granulocytopenia, commonly occurs. The nadir for white blood cell count usually occurs from the ninth to the fourteenth day after initiation of therapy but may occur as late as the twenty-fifth day. The count usually returns to normal by the thirtieth day. Thrombocytopenia may also occur, with the lowest platelet counts occurring from the seventh to the seventeenth day of therapy.

Cardiovascular

Fluorouracil administration has, on occasion, has been associated with angina, myocardial ischaemia, myocardial infarction, cardiomyopathy and very rarely sudden death. There have been reports of chest pain, tachycardia, breathlessness, arrhythmia and ECG changes (ST segment changes) after administration of fluorouracil.

Ophthalmic

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

Neurological

Disorientation, confusion, euphoria, ataxia, dizziness, headache, muscular weakness, nystagmus, slurred speech, unsteadiness and acute cerebellar syndrome. These symptoms may persist after therapy is discontinued.

Combination therapy with fluorouracil and levamisole has been associated with multifocal inflammatory leucoencephalopathy (MILE). Symptoms may include memory loss, confusion, paraethesia, 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.

Infections and Infestations

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

Other

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

DOSAGE AND ADMINISTRATION

General Directions

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

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

Fluorouracil Injection may be administered by intravenous infusion or intravenous injection, the dosage being based on the patient's actual weight. Ideal weight is used only if the patient is obese or if there has been a spurious weight gain due to oedema, ascites or other forms of abnormal fluid retention. Prior to treatment each patient is to be carefully evaluated in order to estimate the optimum initial dosage of fluorouracil.

The total daily dose of fluorouracil should not exceed 1 g. The initial recommended doses should be reduced by one-third to one-half if any of the following conditions are present: poor nutritional state; within 30 days after major surgery; inadequate bone marrow function (white blood cell count < 5,000/ mm^3, platelet count < 100,000/ mm^3); impaired hepatic and/or renal function.

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

Intravenous Infusion

15 mg/kg bodyweight (to a maximum of 1g) daily diluted in 300 to 500 mL of glucose 5% given over a period of four hours. Infusionsshould be continued until the first side effects occur, i.e. stomatitis, diarrhoea leucopenia thrombocytopenia.treatment is thendiscontinued. After the side effects have subsided and the WBC count has risen to 3,000 to 4,000/ mm^3 and the platelet count to 80,000 to 100,000/ $mm^3$the patient should receive maintenance therapy program.

Intravenous Injection

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

Maintenance Therapy

5 to 10mg/kg bodyweight by intravenous injection once a week. Toxic effects rarely occur during maintenance therapy. If, however, they do appear, therapy must be discontinued

until the symptoms regress, otherwise regression of toxic side effects must be awaited before continuing therapy.

Other Methods of Administration

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

Compatibilities

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

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

Overdosage

The possibility of overdosage with fluorouracil is unlikely in view of the mode of administration. Symptoms include nausea, vomiting, diarrhoea, gastrointestinal ulceration and bleeding and bone marrow depression (including thrombocytopenia, leucopenia and agranulocytosis). No specific antidotal therapy exists. Patients who have been exposed to an overdose of fluorouracil should be monitored haematologically for at least four weeks. Should abnormalities appear, appropriate therapy should be utilized.

The Poisons Information Centre, telephone number 131 126, should be contacted for advice on the management of an overdosage.

Handling Precautions

As with all antineoplastic agents, trained personnel should prepare Fluorouracil Ebewe. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling fluorouracil. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed, thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as fluorouracil.

Luer-Lok fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

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

Spills and Disposal

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

PRESENTATION

500 mg in 10 mL glass vial: 1's and 5’s

1000mg in 20 mL glass vial: 1's

2500mg in 50mL glass vial: 1’s

5000mg in 100mL glass vial: 1’s

STORAGE

500mg in 10mL and 1000mg in 20mL - Store at 8°C to 25°C. (Do not refrigerate). Protect from light.

2500mg in 50mL and 5000mg in 100mL - Store below 25°C. Do not refrigerate. Do not freeze. Protect from light.

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

MEDICINE CLASSIFICATION

Prescription Medicine

NAME AND ADDRESS OF SPONSOR

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DATE OF PREPARATION

09 December 2014