FLUOROURACIL INJECTION IP

ZEFLO

COMPOSITION:

Each ml of Zeflo 250/500 mg Injection contains:

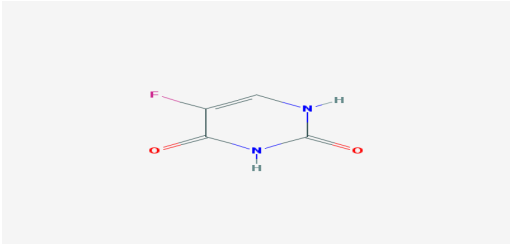
Fluorouracil IP

As Fluorouracil Sodium 50mg

Description

Fluorouracil Injection, an antineoplastic antimetabolite, is a sterile, nonpyrogenic injectable solution for intravenous administration. Each ml contains 50mg fluorouracil in water for injection, pH is adjusted to approximately 9.2 with sodium hydroxide.

Chemically, fluorouracil, a fluorinated pyrimidine, is 5-fluoro-2,4 (1H,3H)-pyrimidinedione. It is a white to practically white crystalline powder which is sparingly soluble in water. The molecular weight of fluorouracil is 130.08 and the structural formula is:



MECHANISM OF ACTION / PHARMACODYNAMICS :

5-Fluorouracil belongs to the antimetabolite class of compounds. It is phase specific with maximal effect on cells in the S-phase. It interferes ith the synthesis of DNA and RNA by inhibiting thymidylate synthase and incorporation of FdUTP into DNA may also affect the DNA stability.

PHARMACOKINETICS

ABSORPTION, DISTIBUTION & ELIMINATION:

5-Fluorouracil is usually administered by intravenous route as the bioavailability by oral route is erratic. It has a primary half-life of 6-20 min. bioavailability is dose dependent and seems to increase with dose, suggestive of a saturable first pass elimination process in the liver. Volume of its distribution slightly

exceeds the extracellular space it is extensively metabolized in the liver and about 90% of conventional dose of 5-Fluorouracil the eliminated by metabolism while less than 5% undergoes renal excretion. In patients with clinically evident hepatic metastasis and liver dysfunction slower clearance and higher plasma levels of Fluorouracil have been reported.

INDICATIONS :

Fluorouracil is indicated in the palliative treatment of carcinoma of the colon, rectum, breast, stomach and pancreas.

DOSAGE AND ADMINISTRATION:

Administration: 5-Fluorouracil is administered intravenously avoiding extravasation, as bolus or infusion after dilution with 5% dextrose solution or normal saline.

Dosage:

Dosage is based on ideal weight. Daily dose, however should not generally exceed 800mg regardless of the weight of the patient. Various dose schedules have been reported in the literature. Dosage must be based on clinical, hematological response and tolerance.

A representative regimen in adequately nourished patients consists of a dose of 12mg/kg given once daily for 4 consecutive days. Toxicity not precluding further therapy a further 6mg/kg dose may be given on 6^{th}, 8^{th}, 10^{th} and 12^{th} day at the end of which therapy is discontinued unless toxicity sets in before, requiring termination of treatment.

In poor risk or inadequately nourished patients an initial dosage of 6mg/kg daily for 3 days has been suggested. If further therapy is not precluded by toxicity a dose of 3mg/kg on day 5, 7 and 9 may be given unless toxicity occurs before. A daily dose of not more than 400mg should be used in poor risk patients.

The above course may be repeated after an interval of 30 days of initiation of therapy subject to toxicity (see warnings & precaution). Alternatively, a weekly dose of 10-15mg/kg (weekly dosage not exceeding 1g) may be used after recovery from toxicity due to initial therapy. The dosage schedule in repeated courses depends on patient's response to initial therapy.

WARNING:

Fluorouracil has a narrow margin of safety because of its low therapeutic index. Hence it should be given by or under the supervision of a physician experienced in cancer chemotherapy and in the use of antimetabolites.

The major toxic effects are on the rapidly proliferating normal tissues particularly the bone marrow and the lining of the gastrointestinal tract, being dose and schedule dependent.

Anorexia, nausea and vomiting are the common adverse effects which can be treated by antiemetics. It may cause stomatitis which is preceded by dryness of mouth, erythema, ulceration and necrosis. The G. I. toxicity can be severe and life threatening with dysphagia, nausea and vomiting, watery diarrhea at times with blood, leading to profound dehydration and hypotension requiring cessation of therapy. Gut line disruption, it coincides with leukocyte nadir after high dose, may lead to sepsis. Supportive care and vigorous hydration in case of severe toxic reaction is indicated.

Leukopenia, predominantly granulocytopenia, thromobocytopenia, and anemia commonly occur during fluorouracil therapy and must be monitored carefully. Generally the nadir of WBC count occurs between day 9-14 of therapy. Hematopoietic recovery is usually rapid and by thirtieth day, blood cell count usually returns to normal. Dermatologic toxicity such as reversible alopecia, dermatitis, nail changes, increased pigmentation, atrophy of the skin, enhance reaction with UV light, photosensitivity, and enhancement of cutaneous toxicity of radiation may occur.

Neurologic symptoms such as somnolence, disorientation, confusion, euphoria, ataxia, headache, and acute cerebellar syndrome have been reported. Ocular effects such as lacrimation, dacryostenosis, visual changes, and photophobia may occur. Myocardial ischemia and angina have been rarely reported, the exact mechanism for which is not known.

PRECAUTIONS:

The drug should be discontinued if the leucocyte count falls below 3500/mm^3 or decreases rapidly or the platelet count is below 100000/mm^3 the patient should be placed in protective isolation and appropriate measures to prevent infection.

Because of non-linear pharmacokinetics at high doses, the plasma concentrations and hence toxicity of fluorouracil is not predictable. In patients with compromised liver function or liver metastasis, the danger of toxicity may be further increased due to slower clearance. There is also greater risk of toxicity in inadequately nourished patients.

It should be used with extreme caution in patients who have previously received high dose pelvic radiation therapy or alkylating agents.

Paediatric Precautions:

Safety and efficacy of 5-Fluorouracil in children has not been established.

ADVERSE REACTONS

Anorexia, nausea and vomiting are the common adverse effects which can be treated by antiemetics. It may cause stomatitis which is preceded by dryness of mouth, erythema, ulceration and necrosis. The G. I. toxicity can be severe and life threatening with dysphagia, nausea and vomiting, watery diarrhea at times with blood, leading to profound dehydration and hypotension requiring cessation of therapy. Gut line disruption, it coincides with leukocyte nadir after high dose, may lead to sepsis. Supportive care and vigorous hydration in case of severe toxic reaction is indicated.

DRUG INTERACTIONS:

Drug interactions are possible. Methotrexate, leucovorin, and PALA have been shown to modify the activity as well as toxicity of fluorouracil. This schedule, sequence and dose dependent and may require dose modifications. In vitro studies, animal studies and limited clinical trials on leucovorin, fluorouracil combination have shown a potentiating effect in colorectal cancer, presumably because of increased stability of FdUMP-Dtmp synthase $CH_2 – FH_2$ complex. The sequence of administration is important, for methotrexate, 5-fluorouracil combination. When methotrexate precedes 5-fluorouracil the combination is synergistic while it becomes antagonistic when the order of administration is reversed.

Overdosage:

In case of overdosage – the possibility is less likely – no specific antidotal therapy exists. The patient should be monitored hematologically for at least 4weels and appropriate therapy should be utilized for the abnormalities which may occur.

CONTRAINDICATIONS:

Fluorouracil is contraindicated in patients with poor nutritional status, depressed bone marrow function, those having potentially serious infections or having undergone a major surgery in the recent past. Considering the potential hazard to the fetus fluorouracil is contraindicated during pregnancy. The treatment is to be discontinued in case of intractable vomiting.

Use During Pregnancy and Lactation:

The drug has been shown to be teratogenic in animal studies at higher dose than maximum recommended human therapeutic doses. It has been shown to cross placenta in rats. Although there is no evidence of fluorouracil being teratogenic in humans, considering other DNA synthesis inhibitors such as methotrexate having shown teratogenicity.

Fluorouracil may have adverse effect on perinatal and postnatal development. Hence women of child bearing age should be advised to avoid pregnancy during fluorouracil therapy. If the drug is during pregnancy or a patient becomes pregnant while receiving therapy, she should be informed of hazards to the fetus.

Nursing of infant during therapy is not recommended considering its ability to inhibit DNA, RNA and protein synthesis and absence of adequate data on its distribution in the milk.

STORAGE:
STORE BETWEEN 15 ºC & 25 ºC
DO NOT FREEZE, PROTECT FROM LIGHT.

PRESENTATION:
5 ml and 10 ml ampoule pack

SINGLE USE PACK:
If separation has occurred, the injection should be warmed to 60ºC, vigorously shaken and allowed to cool to body temperature prior to use.

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
A WHO-GMP CERTIFIED COMPANY
B/111, 112, 113, Kanara Business Centre,
Link Road, Ghatkopar (East), Mumbai 400075.
www.zuviuslifesciences.in