210mm

140mm

Flurosol 500mg/10ml Injection

(Fluorouracil USP)

فلوروسول ۵۰۰ ملی گرام/۱۰ ملی لیٹر انجیکشن

(فلوروریوراسل۔ یو ایس پی)

COMPOSITION:

Flurosol Injection 500mg/10ml

Each 10ml vial contains:

Fluorouracil (USP).....500mg

Product complies USP specs.

DESCRIPTION:

Fluorouracil is an antimetabolite antineoplastic agent; fluorinated pyrimidine antineoplastic agent; toxicities and efficacy of 5-FU differ depending upon the route of administration. It is a colorless to faint yellow, aqueous, sterile, non-pyrogenic injectable solution. It is a chemotherapy medication used to treat various types of cancers including colon, rectum, gastric, pancreatic and breast cancer.

MECHANISM OF ACTION:

Fluorouracil is a nucleoside metabolic inhibitor that interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA); these affect rapidly growing cells and may lead to cell death. Fluorouracil is converted to three main active metabolites: 5-fluoro-2′-deoxyuridine-5′-monophosphate (FdUMP), 5-fluorouridine-5′ triphosphate (FUTP) and 5-fluoro-2′-deoxyuridine-5′-triphosphate (FdUTP). These metabolites have several effects including the inhibition of thymidylate synthase by FdUMP, incorporation of FUTP into RNA and incorporation of FdUTP into DNA.

INDICATIONS:

Fluorouracil is indicated for the treatment of patients with:

- Adenocarcinoma of the Colon and Rectum
- Adenocarcinoma of the Breast
- Gastric Adenocarcinoma
- Pancreatic Adenocarcinoma

DOSAGE AND ADMINISTRATION:

General Dosage Information

Fluorouracil is recommended for administration either as an intravenous bolus or as an intravenous infusion. **Do not inject the entire contents of the vial directly into patients.** Individualize the dose and dosing schedule of fluorouracil based on tumor type, the specific regimen administered, disease state, response to treatment, and patient risk factors.

Recommended Dosage for Adenocarcinoma of the Colon and Rectum

The recommended dose of fluorouracil, administered in an infusional regimen in combination with leucovorin alone, or in combination with leucovorin and oxaliplatin or irinotecan, is 400mg/m² by intravenous bolus on Day 1, followed by 2400mg/m² to 3000mg/m² intravenously as a continuous infusion over 46 hours every two weeks. The recommended dose of fluorouracil, if administered in a bolus dosing regimen in combination with leucovorin, is 500mg/m² by intravenous bolus on Days 1, 8, 15, 22, 29, and 36 in 8-week cycles.

Recommended Dosage for Adenocarcinoma of the Breast

The recommended dose of fluorouracil, administered as a component of a cyclophosphamide-based multidrug regimen, is 500mg/m² or 600mg/m² intravenously on Days 1 and 8 every 28 days for 6 cycles.

Recommended Dosage for Gastric Adenocarcinoma

The recommended dose of fluorouracil, administered as a component of a platinum-containing multidrug chemotherapy regimen, is 200mg/m² to 1000mg/m² intravenously as a continuous infusion over 24 hours. The frequency of dosing in each cycle and the length of each cycle will depend on the dose of fluorouracil and the specific regimen administered.

Recommended Dosage for Pancreatic Adenocarcinoma

The recommended dose of fluorouracil, administered as an infusional regimen in combination with leucovorin or as a component of a multidrug chemotherapy regimen that includes leucovorin, is 400mg/m² intravenous bolus on Day 1, followed by 2400mg/m² intravenously as a continuous infusion over 46 hours every two weeks.

Dose Modifications

Withhold fluorouracil for any of the following:

- Development of angina, myocardial infarction/ischemia, arrhythmia, or heart failure in patients with no history of coronary artery disease or myocardial dysfunction.
- Hyperammonemic encephalopathy.
- Acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances.
- Grade 3 or 4 diarrhea.
- Grade 2 or 3 palmar-plantar erythrodysesthesia (hand-foot syndrome).
- Grade 3 or 4 mucositis.
- Grade 4 myelosuppression.

Upon resolution or improvement to Grade 1 diarrhea, mucositis, myelosuppression, or palmar-plantar erythrodysesthesia, resume fluorouracil administration at a reduced dose. There is no recommended dose for resumption of fluorouracil administration following development of any of the following adverse reactions:

- Cardiac toxicity.
- Hyperammonemic encephalopathy.
- Acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances.

Intravenous administration

The dose of 5-fluorouracil and the treatment schedule depends on the chosen treatment regimen, the indication, the general status and previous treatment of the patient. Treatment regimens vary in the combination of 5-fluorouracil with other cytotoxic agents or dose of concomitantly used folinic acid. The number of cycles used should be decided by the treating clinician depending on local treatment protocols and guidelines; taking into consideration treatment success and tolerability in individual patients. Initial treatment should be given in hospital.

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

Adults and elderly patients receiving 5-fluorouracil should be monitored prior to each dose for hematological (platelet, leucocyte, and granulocyte counts), gastrointestinal (stomatitis, diarrhea, bleeding from the gastrointestinal tract), and neurological toxicity, and, if necessary, the dose of 5-fluorouracil may be either reduced or withheld.

Necessity of dosage adjustment or discontinuation of the medicinal product depends on the occurrence of undesirable effects. Hematological toxicities such as reduced leukocytes (≤ 3500/mm³) and/or platelet counts (≤ 100000/mm³) can require treatment interruption. Resumption of treatment must be decided by the treating clinician depending upon the clinical scenario.

PHARMACOKINETICS:

Following bolus intravenous injection, fluorouracil distributes throughout the body including the intestinal mucosa, bone marrow, liver, cerebrospinal fluid and brain tissue.

Following bolus intravenous injection, 5 – 20 % of the parent drug is excreted unchanged in the urine in six hours. The remaining percentage of the administered dose is metabolized, primarily in the liver. The metabolites of fluorouracil (e.g., urea and α-fluoro-ßalanine) are excreted in the urine over 3 to 4 hours. Following bolus intravenous injection of fluorouracil, as a single agent, the elimination half-life increased with dose from 8 to 20 minutes.

WARNINGS AND PRECAUTIONS:

Increased Risk of Serious or Fatal Adverse Reactions in Patients with Low or Absent Dipyrimidine Dehydrogenase (DPD) Activity

Based on post marketing reports, patients with certain homozygous or certain compound heterozygous mutations in the DPD gene that result in complete or near complete absence of DPD activity are at increased risk for acute early-onset of toxicity and severe, life-threatening, or fatal adverse reactions caused by fluorouracil (e.g., mucositis, diarrhea, neutropenia, and neurotoxicity). Patients with partial DPD activity may also have increased risk of severe, life-threatening, or fatal adverse reactions caused by fluorouracil. Withhold or permanently discontinue fluorouracil based on clinical assessment of the onset, duration and severity of the observed toxicities in patients with evidence of acute early-onset or unusually severe toxicity, which may indicate near complete or total absence of DPD activity. No fluorouracil dose has been proven safe for patients with complete absence of DPD activity. There is insufficient data to recommend a specific dose in patients with partial DPD activity as measured by any specific test.

Cardiotoxicity

Fluorouracil can cause cardiotoxicity, including angina, myocardial infarction/ischemia, arrhythmia, and heart failure, based on post marketing reports. Reported risk factors for cardiotoxicity are administration by continuous infusion rather than intravenous bolus and presence of coronary artery disease. Withhold fluorouracil for cardiotoxicity. The risks of resumption of fluorouracil in patients with cardiotoxicity that has resolved have not been established.

Hyperammonemic Encephalopathy

Fluorouracil can cause hyperammonemic encephalopathy in the absence of liver disease or other identifiable cause, based on post marketing reports. Signs or symptoms of hyperammonemic encephalopathy began within 72 hours after initiation of fluorouracil infusion; these included altered mental status, confusion, disorientation, coma, or ataxia, in the presence of concomitant elevated serum ammonia level. Withhold fluorouracil for hyperammonemic encephalopathy and initiate ammonia-lowering therapy. The risks of resumption of fluorouracil in patients with hyperammonemic encephalopathy that has resolved have not been established.

Neurologic Toxicity

Fluorouracil can cause neurologic toxicity, including acute cerebellar syndrome and other neurologic events, based on post marketing reports. Neurologic symptoms included confusion, disorientation, ataxia, or visual disturbances. Withhold fluorouracil for neurologic toxicity. There are insufficient data on the risks of resumption of fluorouracil in patients with neurologic toxicity that has resolved.

Diarrhea

Fluorouracil can cause severe diarrhea. Withhold fluorouracil for Grade 3 or 4 diarrhea until resolved or decreased in intensity to Grade 1, then resume fluorouracil at a reduced dose. Administer fluids, electrolyte replacement, or antidiarrheal treatments as necessary.

Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome)

Fluorouracil can cause palmar-plantar erythrodysesthesia, also known as hand-foot syndrome (HFS). Symptoms of HFS include a tingling sensation, pain, swelling, and erythema with tenderness, and desquamation. HFS occurs more commonly when fluorouracil is administered as a continuous infusion than when fluorouracil is administered as a bolus injection, and has been reported to occur more frequently in patients with previous exposure to chemotherapy. HFS is generally observed after 8-9 weeks of fluorouracil administration but may occur earlier. Institute supportive measures for symptomatic relief of HFS. Withhold fluorouracil administration for Grade 2 or 3 HFS; resume fluorouracil at a reduced dose when HFS is completely resolved or decreased in severity to Grade 1.

Myelosuppression

Fluorouracil can cause severe and fatal myelosuppression which may include neutropenia, thrombocytopenia, and anemia. The nadir in neutrophil counts commonly occurs between 9 and 14 days after fluorouracil administration. Obtain complete blood counts prior to each treatment cycle, weekly if administered on a weekly or similar schedule, and as needed. Withhold fluorouracil until Grade 4 myelosuppression resolves; resume fluorouracil at a reduced dose when myelosuppression has resolved or improved to Grade 1 in severity.

Mucositis

Mucositis, stomatitis or esophagopharyngitis, which may lead to mucosal sloughing or ulceration, can occur with fluorouracil. The incidence is reported to be higher with administration of fluorouracil by intravenous bolus compared with administration by continuous infusion. Withhold fluorouracil administration for Grade 3 or 4 mucositis; resume fluorouracil at a reduced dose once mucositis has resolved or decreased in severity to Grade 1.

Increased Risk of Elevated International Normalized Ratio (INR) with Warfarin

Clinically significant elevations in coagulation parameters have been reported during concomitant use of warfarin and fluorouracil. Closely monitor patients receiving concomitant coumarin-derivative anticoagulants such as warfarin for INR or prothrombin time in order to adjust the anticoagulant dose accordingly.

Embryofetal Toxicity

Based on its mechanism of action, fluorouracil can cause fetal harm when administered to a pregnant woman. In animal studies, administration of fluorouracil at doses lower than a human dose of 12 mg/kg caused teratogenicity. If this drug is

used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during and for 3 months following cessation of therapy with fluorouracil.

Pregnancy

Pregnancy Category D

There are no adequate and well-controlled studies with fluorouracil in pregnant women. Based on its mechanism of action, fluorouracil can cause fetal harm when administered to a pregnant woman. Administration of fluorouracil to rats and mice during selected periods of organogenesis, at doses lower than a human dose of 12 mg/kg, caused embryo lethality and teratogenicity. Malformations included cleft palate and skeletal defects. In monkeys, maternal doses of fluorouracil higher than an approximate human dose of 12 mg/kg resulted in abortion. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

Nursing Mothers

It is not known whether fluorouracil or its metabolites are present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from fluorouracil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Females and Males of Reproductive Potential

Contraception

Females: Based on its mechanism of action, fluorouracil can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with fluorouracil and for up to 3 months following cessation of therapy.

Males: Fluorouracil may damage spermatozoa. Advise males with female partners of reproductive potential to use effective contraception during and for 3 months following cessation of therapy with fluorouracil.

Infertility

Females: Advice females of reproductive potential that, based on animal data, fertility may be impaired while receiving fluorouracil.

Males: Advice males of reproductive potential that, based on animal data, fertility may be impaired while receiving fluorouracil.

SIDE EFFECTS:

Hematologic disorders:

Myelosuppression, neutropenia, thrombocytopenia, leucopenia, agranulocytosis, anemia and pancytopenia.

Gastrointestinal disorders:

Gastrointestinal adverse events are very common and may be life-threatening. Mucositis (stomatitis, esophagitis, pharyngitis, proctitis), anorexia, watery diarrhea, nausea, vomiting, gastrointestinal ulceration.

Neurologic disorders:

nystagmus, headache, dizziness, symptoms of Parkinson's disease, pyramidal signs, euphoria, somnolence, symptoms of leucoencephalopathy including ataxia, acute cerebellar syndrome, dysarthria, confusion, disorientation, myasthenia, aphasia, convulsion or coma, kidney failure.

Dermatologic disorders:

Alopecia may be seen in a substantial number of cases, particularly females, but is reversible. Palmar-plantar erythrodysesthesia syndrome (hand-foot syndrome) has been noted with protracted and high dose continuous infusion. The syndrome begins with dysesthesia of the palms and soles that progress to pain and tenderness. There is associated symmetrical swelling and erythema of the hand and foot. Dermatitis, skin alterations (e.g. dry skin, fissure erosion, erythema, pruritic maculopapular rash), exanthema, urticaria, photosensitivity, hyperpigmentation of the skin, streaky hyperpigmentation or depigmentation near the veins. Changes in the nails (e.g. diffuse superficial blue pigmentation, hyperpigmentation, nail dystrophy, pain and thickening of the nail bed, paronychia) and onycholyse.

Ophthalmic disorders:

Lacrimal duct stenosis, visual changes, lacrimation, photophobia

Psychiatric disorders:

Euphoria, disorientation

Immune system disorders:

Bronchospasm, immunosuppression with an increased risk of infection, generalized allergic reactions, anaphylaxis, and anaphylactic shock.

Cardiac disorders:

Ischemic ECG abnormalities, Angina pectoris-like chest pain, arrhythmia, myocardial infarction, myocardial ischemia myocarditis, heart insufficiency, dilative cardiomyopathy, cardiac shock, cardiac arrest, sudden cardiac death, cardiotoxic adverse events mostly occur during or within hours following the first treatment cycle. There is an increased risk of cardiotoxicity in patients with previous coronary heart disease or cardiomyopathy.

Hepatobiliary disorders:

Liver cell damage, liver necrosis (cases with fatal outcome), biliary sclerosis, cholecystitis.

Reproductive system disorder:

Spermatogenesis and ovulation disorder

Miscellaneous:

Thrombophlebitis, epistaxis, nail changes (including loss of nails), delayed wound healing, malaise, weakness, fatigue, fever, vein discoloration proximal to injection sites.

DRUG INTERACTIONS:

Anticoagulants and CYP 2C9 Substrates

Elevated coagulation times have been reported in patients taking fluorouracil concomitantly with warfarin. While pharmacokinetic data are not available to assess the effect of fluorouracil administration on warfarin pharmacokinetics, the elevation of coagulation times that occurs with the fluorouracil prodrug Capecitabine is accompanied by an increase in warfarin concentrations. Thus, the interaction may be due to inhibition of cytochrome P450 2C9 by fluorouracil or its metabolites.

Others

- Various agents have been reported to biochemically modulate the anti-tumour efficacy or toxicity of Fluorouracil. Common drugs include methotrexate, metronidazole, leucovorin interferon Alfa and allopurinol.
- Both the efficacy and toxicity of 5-fluorouracil may be increased when 5-fluorouracil is used in combination with folinic acid. Side effects may be more pronounced and severe diarrhea may occur. Life-threatening diarrheas have been observed if 600 mg/m² of fluorouracil (IV bolus once weekly) is given together with folinic acid.
- In combination with other myelosuppressive substances, dosage adjustment is necessary. Concomitant or previous radiation therapy may require dosage reduction. The cardiotoxicity of anthracyclines may be increased.
- Fluorouracil should be avoided in combination with clozapine due to increased risk of agranulocytosis.
- Increased incidence of cerebral infarction has been reported in oropharyngeal cancer patients treated with fluorouracil and cisplatin.
- Marked elevations of prothrombin time and INR have been reported in a few patients stabilized on warfarin therapy following initiation of fluorouracil regimes.
- The enzyme dihydropyrimidine dehydrogenase (DPD) plays an important role in the metabolism of fluorouracil. Nucleoside analogues, e.g. brivudin and sorivudin, may induce an increase in plasma concentrations of 5-FU or other fluoropyrimidines accompanied by toxicological reactions. Therefore, a time interval of minimum 4 weeks between administration of fluorouracil and brivudin, sorivudin and analogues should be kept.
- If applicable, determination of DPD enzyme activity is indicated prior to treatment with 5- fluoropyrimidines.
- Cimetidine, metronidazole and interferon may increase the plasma level of 5-fluorouracil, thereby increasing the toxicity of 5-fluorouracil.
- In patients receiving phenytoin and fluorouracil concomitantly, an increase of phenytoin plasma concentration has been reported resulting in symptoms of phenytoin toxicity.
- Fluorouracil enhances the action of other cytostatic drugs and irradiation therapy.
- In patients receiving cyclophosphamide, Methotrexate and 5-fluorouracil, addition of thiazide diuretics resulted in a more pronounced decrease of the number of granulocytes when compared to patients not receiving thiazides.
- Hepatotoxicity (increase in alkaline phosphatases, transaminases or bilirubin) has been observed commonly in patients receiving 5-fluorouracil in combination with levamisol.
- In patients with breast cancer, combination therapy with cyclophosphamide, methotrexate, 5-fluorouracil and tamoxifen has been reported to increase the risk of thromboembolic events.
- Serious, potentially life-threatening mucositis may occur following co-administration of vinorelbine and 5-fluorouracil/folinic acid.
- Vaccination with live vaccines should be avoided in immunocompromised patients.

CONTRAINDICATIONS:

Hypersensitivity to the fluorouracil or to any of the excipients.

Fluorouracil is contraindicated in the following:

- Serious infections (e.g. Herpes zoster, chickenpox).
- Seriously debilitated patients.
- Bone marrow depression after radiotherapy or treatment with other antineoplastic agents.
- Management of non-malignant disease.
- Serious liver impairment.
- Fluorouracil (5-FU) must not be given in combination with brivudin, sorivudin and analogues. Brivudin, sorivudin und analogues are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Fluorouracil (5-FU) must not be given to patients homozygotic for dihydropyrimidine dehydrogenase (DPD).
- Fluorouracil is strictly contraindicated in pregnant or breast feeding women.

Known complete dihydropyrimidine dehydrogenase (DPD) deficiency.

OVER DOSAGE:

Administer uridine triacetate within 96 hours following the end of fluorouracil infusion for management of fluorouracil overdose.

STORAGE & INSTRUCTIONS:

Store between 20-25°C. Protect from heat and sunlight. Do not freeze. Keep away from the reach of children. Retain in carton until time of use.

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

To be sold on the prescription of a registered oncologist or on demand from cancer hospitals and institutions only.

HOW SUPPLIED:

10ml x 1's, 10ml x 5's, 10ml x 10's.

خوراک وطریقہ استعمال:

سرطان کے ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۲۰-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔

دوا کو دھوپ، گرمی اور منجمد ہونے سے بچائیں۔

بچوں کی پہنچ سے دور رکھیں۔

صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخے پر فروخت کریں۔ صرف وریدی استعمال کیلئے۔

Manufactured by:

PHARMASOL

PRIVATE LIMITED

Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.