PHARMAURACIL

Fluorouracil 250mg & 500mg Injection
Antineoplastic

فارمایوراسل انجکشن

فلوروریوراسل 500/250 ملی گرام

Action And Clinical Pharmacology: There appear to be 2 mechanisms of action of fluorouracil which result in cyotoxic effects. One is the competitive inhibition of thymidylate synthetase, the enzyme catalyzing the methylation of deoxyuldylic acid to thymidylic acid. The consequent thymidine deficiency results in inhibition of deoxyribonucleic acid (DNA) synthesis, thus inducing cell death. A second mechanism of action is evidenced by the moderate inhibition of ribonucleic acid (RNA) and incorporation of fluorouracil into RNA. The predominant mechanism of antitumor action appears to be dependent at least in part on individual tumor intracellular metabolism.

The effects of DNA and RNA deprivation are most significant on those cell which are most rapidly proliferating.

Following i.v. injection, fluorouracil is cleared rapidly from the plasma (half-life about 10 to 20 minutes),and distributed throughout body tissues including the cerebropinal fluid and malignant effusions, exhibiting a volume of distribution equivalent to the total body water. Plasma concentrations fall below measurable levels within 3 hours. Oral administration of fluorouracil has shown marked vanability in its bioavailbility, from 28 to 100%. Constant i.v. infusion for 96 hours showed constant plasma drug levels and significantly (50 to 1000 fold) less drug in bone marrow. Fluorouracil is converted to active nucleotide metabolites, 5-fluorouridine monophosphate and 5-fluorodeoxyuridylate within the target cell itself. Approximately 20% of an i.v. dose is excreted intact in the urine within 6 hours. The remainder is catabolized primarily in the liver where enzymatic cleavage yields a-fluoro-b-alanine, respiratory carbon dioxide, urea and ammonia. The non-linearity of fluorouracil pharmacokinetics are related to saturation of its degradation.

Indications And Clinical Uses: In the palilative treatment of colorectal carcinoma, and carcinoma of the breast, and in the treatment of carcinoma of the stomach, pancreas, prostate, ovary, bladder , head and neck, either as a single agent or in combination with radiation therapy, and/or other chemotherapeutic agents. Listed below are tumor types and drugs used concurrently with fluorouracil, Carclnoma of the Breast: Fluorouracll with cyclophosphamide and doxorubicin; fluorouracil with cyclophosphamide and epirubicin; fluorouracil with cyclophosphamide and doxorubicin vincristine and prednisone; cyclophosphamide, methotrexate and fluorouracil (CMF) for advanced disease as well as in the adjuvant setting of breast cancer

Carclnoma of the Stomach: Fluorouracil with doxorubicin and mitomycin-C

Carcinoma of the pancreas: Fluorouracill with doxorubicin and mitomycin-C fluorouracil with mitomycin-C and streptozotocin.

Cancer of the Urinary Bladder: Fluorouracil alone; fluorouracil with doxorubicin; fluorouracil with doxorubicin and cisplatin; fluorouracil with doxorubicin and cyclophosphamide fluorouracil with methotrexate, cyclophosphamide and vincristine.

Carcer of the Prostate: Fluorouracil alone: fluorouracil with doxorubicin and cyclophosphamide.

Cancer of the Head and Neck: Fluorouracil with cisplatin: fluorouracil with carboplatin.

Cancer of the Ovary: Fluorouacil with hexamethylmelamine, cyclophosphamide and doxorubicin.

No studies performed to date have shown malignant melanoma, kidney carcinoma, the leukemias and lymphomas, soft tissue and bone sarcomas, bronchogenic carcinoma, brain tumors and metastases to the CNS to be significantly responsive to fluorouracil therapy.

Also indicated as adjuvant therapy in colorectal and breast cancer.

Colorectal Cancer: Comparisons between patients receiving postoperative adjuvant chemotherapy and those treated by curative surgical resection alone have shown improved response rates and an overall improvement in disease free survival in favor of the adjuvant chemotherapy groups.

Effective treatments have included fluorouracil In combinaiton with other chemotherapeutic agents (semustine and vincristine for example) and fluorouracil with leucovprin modulation (the Machover regime for example), in patients with Dukes's B and C colon cancer.

Breast Cancer: Several studies of adjuvant chemotherapy have demonstrated a moderate reduction in the risk of recurrence in patients with primary operable breast cancer.

The most common chemotherapeutic regimens is cyclophosphamide methotrexate and 5-fluorouracil (CMF) in estrogen-receptor-negative patients, with the addition of tamoxifen in estrogen-receptor-positive patients. A regime comprising fluorouracil doxorubicin and cyclophosphamide (FAC) as adjuvant chemotherapy has also been found to be effective , although with risk of doxorubicin cardiotoxicity. Not intended to be used prophylactically.

Contra-Indications: Patients who are debilitated or who have poor nutritional state, depressed bone marrow function following radiotherapy or therapy with other antineoplastic agents, or potentially serious infections, or with known hypersensitivity to the drug.

Manufacturer's Warnings In Clinical States: Caution: Fluorouracil is a potent drug and should be administered by, or under supervision of a physician who is experienced in cancer chemotherapy.

It is recommended that fluorouracil be given only by or under supervision of a physician who is well acquainted with the use of potent antimetabolites. 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 tumors, or who have impaired hepatic or renal function. 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 deprsses the bone marrow function, will increase the toxicity of fluorouracil.

Pregnancy and Reproductive Effects: Since fluorouracil is known to be teratogenic in animals, the drug should not be used during pregnancy, particularly in the first trimester, unless the potential benefits to the patient outweigh the hazards. Because the risk of mutagenesis has not been evaluated, such possible effects on males and females must be considered.

Lactation: It is not known whether fluorouracil is excreted in human milk. Because fluorouracil inhibits DNA RNA and protein synthesis, mothers should not nurse while receiving this drug.

Precautions: General: Fluorouracil is a cytotoxic drug with a narrow margin of safety. Patients should be advised that therapeutic response is unlikely to occur without some evidence of toxicity.

Leukocyte counts with differential and platelet counts are recommended before each dose, and hematologic status monitored during therapy.

Prompts cessation of fluorouracil therapy should be considered if any of the following signs appear: stomatitis or esophagopharyngitis (at the first visible sign of small ulceration at the inner margin of the lips). intractable vomiting, diarrhea (watery stools or frequent bowel movements), gastrointestinal ulceration or bleeding, hemorrhage from any site, leukopenia (WBC<3 500/mm3) or rapidly dropping WBC count, granulocytopenia (under 1500 mm3), thrombocytopenia (platelets <100 000/mm3) Fluorouracil should be resumed only when the patient has recovered from the above signs.

Flurorouracil should be used with caution in patients with impaired liver function and in patients with jaundice.

Drug Interactions: Various purines, pyrimidines and antimetabolites have shown biochemical modulation of fluorouracil in in-vitro test sytstems. Purines include inosine guanosine, guanosine-5-phosphate and deoxyinosine, Pyrimidnes include thymidine, uridine and cytidine. Antimetabolites include methotrexate, tamoxifen, interferon, PALA, allopurinol hydroxyurea, dipridamol and leucovorin. 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 of the fluorouracil component. Fluorouracil causes a change in the spectrophotometric spectrum of cytarabine possibly reducing its effectiveness. Flurouracil mixed with methotrexate alters the spectra of both agents. Fluorouracil is physicallly incompatible with doxorubicin epirubicin and with diazepam; a precipitate forms when fluorouracil is mixed with these drugs. It is recommended that complete i.v. line flushing takes place between injections of fluorouracil and cytarabine, methotrexate, doxorubicin, epirubicin or diazepam.

Laboratory Tests: Increases in serum-total-thyroxine (TT4) and serum-total-triiodothyronine (TT3) levels in euthyroid patients with advanced mammary carcinoma treated with fluorouracil used in a single drug schedule have been reported. The levels returned to pre-treatment levels within 4 weeks of the end of treatment.

Adverse Reactions: The major-toxic effects of fluorouracil occur on the normal, rapidly proliferating tissues, especially those of the bone marrow and lining of the gastrointestinal tract. Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration). diarrhea, anorexia and emesis are common.

Hematological: Myelosuppresions almost uniformly accompanies a course of adequate therapy with fluorouracil. Low WBC counts are usually first obseved between the ninth and fourteenth day after the first course of treatment with the nadir occurring during the third week, although at times delayed for as long as 25 days. By the thirtieth day the count is usually within the normal range. Thrombocytopenia may also occur.

A low grade hemolytic-uremic state. exacerbated by blood transfusions, has been associated with long term therapy with fluorouracil with mltomycin-C

Gastrointestinal: Anorexia and nausea are some of the earliest untoward symptoms during a course of therapy and generally occur during the first week. Those reactions are followed shortly after by stomatitis and diarrhea, which constitute reliable warming signals that sufficient dose has been administered. Esophagitis has also been reported. A Mallory-Weiss lesion following i.v. fluorouracil in combination chemotherapy has also been observed.

Dematological: Alopecia and dermatitis are seen in a substantial number of cases and patients should be advised of this consequence of treatment. The alopecia is reversible. The dermatitis is often a pruritic maculopapular rash generally appreaing on the extramities and less frequently on the trunk. It is usually reversible and responsive to symptomatic treatment. Palmarplantar erythrodysesthesia has been reported in association with the continous infusion of fluorouracil. Dry skin and fissuring have also been noted.

Photosensitivity manifested by erythema or increased skin pigmentation, and nail changes including banding or loss of nails and vein discoloration proximal to injection sites, may occasionally occur.

Others: Chest pain, which ranges from mild angina to crushing pain indistinguishable from that of myocardial infarction, has been reported. This may reoccur with subsequent doses of fluorouracil.

Fewer than 1% of patients receiving fluorouracil will have ataxia or other manifestations of acute cerebellar syndrome due to drug neurotoxicity, although the incidence increases when high doses or intensive daily regimes are used. The dysfunction is completely reversible and may not occur when the drug is reintroduced. Oculomotor disturbances expressed primarily as weakness of convergence and divergence, associated with neurotoxicity, have been noted.

Excessive lacrimation, which gradually appears after fluorouracil treatment and persists thyoughout treatment with the drug, has been reported.

Symptoms And Treatment Of Overdose: Symtoms and Treatment: Daily doses of fluorouracil of 30 mg/kg/day (1.1 to 1.2 g/m2/day) by 5 day continuous infusion have been tolerated. At 35 mg/kg/day. 7 out of 8 patients developed severe stomatitis.

Administration of fluorouracil should be discontinued promptly on the occurrence of stomatitis, or esopharyngitis, leukopenia or rapidly falling WBC count, thrombocytopenia, intractable vomiting, diarrhea, gastrointestinal ulceration and bleeding, or hemorrhage (see Precautions).

Nausea and vomiting may be alleviated by antiemetics. Chronic overdosage may give rise to serious myelosuppression. Daily hematological evaluation should be performed to prevent overdosage. Transfusions of blood or platelets should be give at any sign of hemorrhage. Patients should be carefully observed for intercurrent infection and if present, appropriate antibiotic therapy should be instituted promptly.

Dosage And Administration: Patient Selection: In order to be considered for fluorouracil therapy, a prospective patient should satisfy the following conditions: Good dietary intake with no protein loss. No major surgery within the past 30 days. No history of high dose irradiation to bone-marrow bearing areas of the body (pelvis spine, ribs, etc.) Good or adequate marrow recovery after prior use of a myelosuppressive regime. No serious infections. Adequate renal hepatic functions. Adequate bone marrow function (leukocyte count 5 000/mm3 or over; platelet count 100 000/mm3 or over).

General Dosage and Administration Recommendations: May be administered by i.v. infusion or i.v. injection, taking care to avoid extravasation. No dilulion of fluorouracil injection is required when given by direct i.v. injection . Doasage is normally based on the patient's weight. However, if the patients is obese or there has been a spurious weight gain because of edema, ascites or other forms of adnormal fluid retention, the idea weight or estimated lean body mass should be used. In order to obtain optimum therapeutic results with minimal adverse effects, dosage must be based on the clinical and hematologic response and tolerance of the patient It is thus recommended that each patient be care fully evaluated prior to therapy to estimate accurately the optimum initial dosage of fluorouracil.

Initial Therapy: See Contrainications, Warnings and Precautions. Daily dosage generally should not exceed 800 mg. In good risk patients, a dose of 12 mg/kg (500 mg/m2) via injection is given daily for 5 days and repeated every 28 days. In poor risk patients a dose of 6 to 10 mg/kg (250 to 400 mg/m2) is givn daily for 5 days and repeated every 28 days. When used in combination and with other chemotherapeutic agents, various schedules may be used including a single dose per course a dose on day and day 8 and daily for 4 or 5 days. The dose given varies, depending on the regimen used.

A sequence of 1 to 5 injections constitutes a course of therapy. Therapy should be discontinued promptly when any of the signs of toxicity listed under Precautions appears.

Administration by infusion may result in slightly less toxicity. Diluted solutions (see Dilution for infusion solutions) of fluorouracil injection may be given each day in an i.v. drip infusion, over a period of 4 hours. The dosages should be 12 mg/kg or 480 mg/m2 daily for most patients (maximum 800 mg/day).or 6 mg/kg or 240 mg/m2 daily for poor-risk patients (maximum 400 mg/day). These infusions should be continued daily until gastrointestinal side effects appear, which is usually the case after 8 to 15 days.

Fluorouracil may also be administered by continuous 24 hour, intra-arterial infusion, at a dosage of 5 to 7.5 mg/kg/day.

Maintenance Therapy: When toxicity has not been a problem, or after the toxic signs from the initial course of therapy have subsided, therapy should be continued using either of the following schedules: Repeat dosage of the first course, beginning 28 days after the first day of the previous course of treatment . Administer a maintenance dosage of 10 to 15 mg/kg/week.

Use reduced dosages for poor risk patients.

The drug dosage to be used should take into accont the patient's reaction to the previous course of therapy and be adjusted accordingly. Some patients have received from 9 to 45 courses of treatment during periods which ranged from 12 to 60 months.

Fluorouracil and Fluorouracil/Leucovorin as Adjuvant Therapy for Colon Cancer: The combination of fluorouracil and Leucovorin has been compared to single agent fluorouracil in several clinical trials for the adjuvant treatment of colorectal cancer, Fluorouracil . as a single agent was delivered at an approximate dose of 530mg/m2/week, while fluorouracil with leucovorin (200 to 500 mg/m2/day) was delivered at an appproximate dose of 462 mg/m2/week.

When used with leucovorin, fluorouracil administered at the single-agent maximum tolerated dose, has occasionally produced unacceptable toxicity. Nevertheless lower doses of fluorouracil when combined with leucovorin, have shown higher response rates than fluorouracil alone.

Cyclophosphamide, Methotrexate and Fluorouracil (CMF) Regimen for Adjuvant Therapy of Breast Carcinoma: Adjuvant chemotherapy with a radical or modified mastectomy in early breast cancer has been shown (statistically) to protect against the development of new primary tumors. The most common chemotherapeutic regimen is cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in estrogen-receptor-negative patients, with the addition of tamoxifen in estrogen-receptor-positive patients.

A typical CMF dosage regimen and schedule is 12 courses of cytclophosphamide 100 mg/m2 orally on days 1 to 14 , methotrexate 40 mg/m2 i.v. on days 1 and 8, and 5-fluorouracil 600 mg/m2 i.v. on days 1 and 8 . Tamoxifen , 10 mg twice a day orally is added in the case of node-positive patients.

Dilution for Infusion Solutions: Fluorouracil injection may be diluted for i.v. infusion, to a final concentration of 2 mg/mL in 5% Dextrose injeiton, in plastic infusion bags or bottles. Dilution should be made just prior to administration and the solution used within 24 hours. Unused solution should be discarded after that time, in order to avoid the risk of microbial contamination.

Fluorouracil injection should not be mixed directly with other chemotherapeutic agents or i.v. additives.

As with all parenteral drug products i.v. admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should not be used.

Special Instructions for Safe Handling: Fluorouracil is a cytotoxic drug and should be handled with extreme caution by experienced personnel. Moreover, fluorouracil is an irritant, and care should be taken to avid contact with the skin and mucous membranes. It is thus recommended that personnel wear PVC gloves, Safety glasses, disposable gowns and masks when carrying out dillutions of fluorouracil. All needles, syringes, ampuls, vials and other material which have come in contact with fluorouracil should be destroyed by incineration at 1' 0000C or more. (Note: Sealed containers may explode). If incineration is not possible, fluorouracil should be detoxified by addition of 0.1 M sodium hydroxide solution or sodium hypochlorite solution (household bleach). placed in sealed containers and deposited in landfill sites or in accordance with local regulations.

Adsorption to Administration Equipment: The stability of fluorouracil is greater in plastic containers than in low grade glass containers, due to adsorption of the drug to glass surfaces. It is suggested that deactivated glass surfaces such as those found in silanized glass be used to prevent drug loss due to adsorption. Fluorouracil does not adsorb to PVC tubing, polyethylene tubing, silastic tubing, polypropylene barrels or polyethylene plungers of plastic syringes.

Warning:

As with all parenteral drug products, I.V admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration. Solutions showing such should not be used.

Availability And Storage: Each mL of sterile solution contains: fluorouracil 25 mg in water for injection. The pH of the solution is adjusted to approximately 9 with sodium hydroxide. Preservative-free. Single dose vials of 250mg/10ml & 500mg/20ml each vial. Packs of 20 vials. Store at temperature not exceeding 25°C it should not be refrigerated. In longer storage of the injection, the solution may discolor slightly, the potency and safety are not adversely affected.

کمرے کے درجہ حرارت (15-25°C) پر خشک جگہ سٹور کریں۔

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تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

صرف مستند ڈاکٹر کے نسخہ پر فراہم کریں۔

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