Flurotor® IV Injection

Fluorouracil Injection USP

DESCRIPTION

Flurotor® IV Injection is a preparation of Fluorouracil. There appears to be two mechanisms of action of Fluorouracil which result in cytotoxic effects. One is the competitive inhibition of thymidylate synthetase, the enzyme catalyzing the methylation of deoxyuridylic 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.

INDICATIONS

Palliative treatment-

- **Carcinoma of the breast:** Fluorouracil 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.
- **Carcinoma of the stomach:** Fluorouracil with Doxorubicin and Mitomycin-C.
- **Carcinoma of the pancreas:** Fluorouracil 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.
- **Cancer 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:** Fluorouracil with Hexamethylmelamine, Cyclophosphamide and Doxorubicin.

Adjuvant therapy-

- **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 combination with other chemotherapeutic agents (Semustine and Vincristine for example) and Fluorouracil with Leucovorin modulation in patients with Duke'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 regimen 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.

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 and hepatic functions
- Adequate bone marrow function (leukocyte count 5,000/mm^3 or over; platelet count 100,000/mm^3 or over)

General dosage and administration recommendations:

Fluorouracil injection may be administered by intravenous infusion or intravenous injection, taking care to avoid extravasation. No dilution of Fluorouracil injection is required when given by direct intravenous injection. Dosage is normally based on the patient's weight. However, if the patient is obese or there has been a spurious weight gain because of edema, ascites or other forms of abnormal fluid retention, the ideal 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 carefully evaluated prior to therapy to estimate accurately the optimum initial dosage of Fluorouracil.

Initial therapy:

Daily dosage generally should not exceed 800 mg. In good risk patients, a dose of 12 mg/kg (500 mg/m^2) 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/m^2) is given daily for 5 days and repeated every 28 days. When used in combination with other chemotherapeutic agents, various schedules may be used including a single dose per course, a dose on day 1 and day 8 and daily for 4 or 5 days. The dose given varies, depending on the regimen used.

Administration by infusion may result in slightly less toxicity. Diluted solutions of Fluorouracil injection may be given each day in an intravenous drip infusion, over a period of 4 hours. The dosages should be 12 mg/kg or 480 mg/m^2 daily for most patients (maximum 800 mg/day), or 6 mg/kg or 240 mg/m^2 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 - 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 account 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 530 mg/m^2/week, while Fluorouracil with Leucovorin (200 to 500 mg/m^2/day) was delivered at an approximate dose of 462 mg/m^2/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 Cyclophosphamide 100 mg/m^2 orally on days 1 to 14, Methotrexate 40 mg/m^2 intravenously on days 1 and 8, and 5-Flourouracil 600 mg/m^2 intravenously on days 1 and 8. Tamoxifen, 10 mg twice a day orally, is added in the case of node-positive patients.

CONTRAINDICATIONS

- Poor nutritional state
- Depressed bone marrow function following radiotherapy or therapy with other antineoplastic agents
- Potentially serious infections
- Hypersensitivity

SIDE EFFECTS

- Esophagopharyngitis
- Nausea, diarrhea, stomatitis
- Anorexia and fatigue

WARNING AND PRECAUTION

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 depresses the bone marrow function, will increase the toxicity of Fluorouracil.

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.

USE IN PREGNANCY AND LACTATION

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

PHARMACEUTICAL PRECAUTION

Do not store above 25 ˚C temperature. Keep away from light and wet place. Keep out of reach of children. Avoid refrigeration (2-8 ˚C temperature). Wear gloves at all times when handling containers.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Although the Fluorouracil solution may discolor slightly during storage, the potency and safety are not adversely affected. 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.

Storage after dilution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C with Glucose 5% or Sodium Chloride 0.9% Injection or Water for Injections at concentration 0.98 mg/mL of Fluorouracil.

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 24 hours at 2-8 °C, unless dilution has been taken place in controlled and validated aseptic conditions.

Spill and Disposal:

In the event of spillage, operators should put on gloves, face mask, eye protection and disposable apron and mop up the spilled material with an 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

PACKAGING

Flurotor® 250 IV Injection : Each box contains one single dose vial of Fluorouracil USP 250 mg / 5 mL injection.

Flurotor® 500 IV Injection : Each box contains one single dose vial of Fluorouracil USP 500 mg / 10 mL injection.

SK+F ONCOLOGY

Manufactured by
ESKAYEF PHARMACEUTICALS LIMITED
RUPGANJ, NARAYANGANJ, BANGLADESH

R/PM0554 V01