For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

FLURAC INJECTION 50 mg/ml

(Fluorouracil Injection BP 50 mg/ml)

For Intravenous use only

Composition:
Each ml contains:
Flurorouracil Ph.Eur. (as Fluorouracil Sodium) ....50 mg.
Water for Injections Ph. Eur. Q.S.

Pharmaceutical Form
Solution for injection

Product Description
A clear, colourless to almost colourless solution in a clear glass vial. When examined under suitable conditions of visibility it should be practically free from particles.
Description after dilution: Clear, colorless solution

Chemistry:
Molecular Formula: $C_4H_3FN_2O_2$. Chemically, Fluorouracil, a fluorinated pyrimide, is 5-fluoro-2, 4 (1H, 3H)-pyrimidinedione. It is a white to practically white crystalline powder which is sparingly soluble in water.
Molecular Weight: 130.08

Pharmacological classification:
Antimetabolite, antineoplastic agent.

Clinical Pharmacology:
There is evidence that the metabolism of Flurac in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. In this manner Flurac interferes with the synthesis of deoxyribonucleic acid (DNA) and to a lesser extent inhibits the formation of ribonucleic acid (RNA). Since DNA and RNA are essential for cell division and growth, the effect of Flurac may be to create a thymine deficiency which provokes unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked in those cells which grow more rapidly and which take up Flurac at a more rapid rate.

Following intravenous injection, Flurac distributes into tumors, intestinal mucosa, bone marrow, liver and other tissues throughout the body. In spite of its limited lipid solubility, Flurac diffuses readily across the blood-brain barrier and distributes into cerebrospinal fluid and brain tissue.

Seven to twenty percent of the parent drug is excreted unchanged in the urine in six hours; of this over 90% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver. The catabolic metabolism of Flurac results in degradation products (eg. CO_2, urea and alfa-fluoro-beta-alanine) which are inactive. The inactive metabolites are excreted in the urine over the next 3 to 4 hours.

Following intravenous administration of Flurac, the mean half-life of elimination from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent.

Indications:
Flurac is indicated 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. Flurac should only be used when other proven measures have failed or are considered impractical.

Contraindications:
Flurac is contra-indicated in patients with bone marrow depression after radiotherapy or treatment with other antineoplastic agents.

Warning & Precautions:
It is recommended that Flurac be given only by or under strict supervision of a qualified physician who is well acquainted with the use of potent metabolites. Because of the possibility of severe toxic reactions, all patients should be hospitalized, at least during the initial course of therapy. Flurac should not be re-administered after a documented cardiovascular reaction (arrhythmia, angina, ST segment changes) as there is a risk of sudden death.
Rarely, severe and unexpected toxic reactions (including stomatitis, diarrhea, neutropenia and neurotoxicity) have been reported in association

with Flurac. These reactions have been attributed to deficiency of dipyrimidine dehydrogenase activity, which appears to cause prolonged clearance of Flurac.
Any form of therapy that adds to the stress of the patient, interferes with nutritional uptake or depress bone marrow function, will increase the toxicity of Flurac.
Adequate treatment with Flurac is usually followed by leucopenia, the lowest white blood cell (WBC) count commonly being observed between the 9th and 14th day of the first course, but occasionally being delayed for as long as 20 days. The count usually returns to normal by the 30th day. Daily monitoring of platelet and WBC counts are recommended and treatment should be stopped if platelets fall below 100,000 per mm^3 or the WBC count falls below 3500 per mm^3. If the WBC count falls below 2000 per mm^3, it is recommended that the patients be placed in protective isolation in the hospital and given the appropriate preventative treatment for systemic infection.
Treatment should also be discontinued at the first sign of oral ulceration or if there is evidence of gastrointestinal side effects such as stomatitis, diarrhea, bleeding from the gastrointestinal tract, oesophagopharyngitis or intractable vomiting.
The ratio between effective and toxic dose is small and therapeutic response is unlikely without some degree of toxicity. Care must be taken, therefore, in the selection of patients and adjustment of dosage.
Flurac should be used with caution in patients with reduced renal or liver function, jaundice or heart disease.
Flurac 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 Flurac based chemotherapy.
Close monitoring for multiple organ toxicities and vigorous supportive care of those with toxicity are necessary.
Combination chemo-or radiotherapy may depress bone marrow function and increase the toxicity of Flurac. Extreme caution is necessary when administering fluorouracil to patients who have had high dose pelvic irradiation, or have been previously treated with alkylating agents.

Pregnancy
Category D. Flurac may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Flurac administered parenterally has been shown to be teratogenic in mice, rats and hamsters, and embryolethal in monkeys. Flurac is strictly contraindicated in pregnancy.

Use in lactation
It is not known whether Flurac is excreted in breast milk. To avoid possible harmful effects in the infant, breast-feeding is not advised during Flurac therapy.

Drug Interactions:
Leucovorin calcium may enhance the toxicity of Flurac.

Combination Therapy
Any form of therapy which and to the stress of the patient, interferes with nutrition or depresses bone marrow function will increase the toxicity of Flurac.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Dosage and Administration:
Mode of administration:
Flurac injection is given as Intravenous injection and Intravenous infusion. Flurac injection, requires dilution before administration as infusion.

General directions
Flurac 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.

The total daily dose of Flurac should not exceed 1 gram. The initial recommended doses should be reduced by one third to a half if any of the following conditions are present:
(1) poor nutritional state
(2) after major surgery (within previous 30 days)
(3) inadequate bone marrow function (WBC count less than 5,000 per mm^3; platelet count less than 100,000 per mm^3)
(4) impaired hepatic and/or renal function

The following regimens have been recommended for use of Flurac as a single agent in adults:

Intravenous infusion

15 milligrams/kg body weight diluted in 300 to 500 mL of 5% glucose given over a period of 4 hours. The infusion may be repeated daily until the first gastrointestinal side effects (eg. Stomatitis, diarrhoea) or haematological side effects (eg. Leucopenia, thrombocytopenia) appear.

Treatment must be discontinued until the side effects have receded (until the WBC count has risen to 3,000 to 4,000 per mm^3 and the platelet count to 80,000 to 100,000 per mm^3). The patient may then be placed on a maintenance therapy program.

Intravenous injection

12 milligrams/kg body weight daily for 3 consecutive days.

Providing there are no signs of toxic effects, the patient may then be given 6 milligrams/kg intravenously on the 5th, 7th and 9th days.

If after the 9th day there is still no sign of toxicity, the patient may be placed on maintenance therapy. In all instances toxic side effects must resolve before maintenance therapy is started.

Maintenance therapy

5 to 10 milligrams/kg body weight by intravenous injection once a week. Toxic symptoms seldom occur during maintenance therapy. If, however, they do appear, therapy must be discontinued until the symptoms resolve.

Other methods of administration

Flurac may be used in combination with other cytotoxic agents or with radiotherapy. In such cases doses should be correspondingly reduced.

Flurac Injection may also be administrated as a 24 hour intra-arterial continuous drip infusion (5 to 7.5 milligrams/kg bodyweight daily).

Adverse Effects:

Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are commonly seen during therapy.

Leukopenia usually follows every course of adequate therapy with Flurac. The lowest white blood cell counts are commonly observed between the 9th and 14th days after the first course of treatment, although uncommonly the maximal depression may be delayed for as long as 20 days. By the 30th day the count has usually returned to the normal range.

Alopecia and dermatitis may be seen in a substantial number of cases. The dermatitis most often seen is a pruritic, maculopapular rash usually appearing on the extremities and less frequently on the trunk. It is generally reversible and usually responsive to symptomatic treatment.

Other adverse effects are:

Hematologic: pancytopenia, thrombocytopenia, agranulocytosis, anemia.

Cardiovascular: myocardial ischemia, angina.

Gastrointestinal: gastrointestinal ulceration and bleeding.

Allergic reactions: anaphylaxis and generalized allergic reactions.

Neurologic: acute cerebellar syndrome (which may persist following discontinuance of treatment), nystagmus, headache.

Dermatologic: dry skin, fissuring, photosensitivity, as manifested by erythema or increased pigmentation of the skin, vein pigmentation; palmar-plantar erythrodysesthesia syndrome, as manifested by tingling of the hands and feet following by pain, erythema, and swelling.

Ophthalmic: Lacrimal duct stenosis, visual changes, lacrimation, photophobia.

Psychiatric: disorientation, confusion, euphoria.

Miscellaneous: thrombophlebitis, epistaxis, nail changes (including loss of nails).

Overdosage:

The possibility of overdosage with Flurac is unlikely in view of the mode of administration. Nevertheless, the anticipated manifestations would be nausea, vomiting, diarrhea, gastrointestinal ulceration and bleeding, bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). No specific antidotal therapy exists. Patients who have been exposed to an overdose of Fluorouracil should be monitored hematologically for at least four weeks. Should abnormalities appear, appropriate therapy should be utilized.

Effects on Ability to Drive and Use Machine:

No studies on the effects on the ability to drive and use machinery have been performed.

Fluorouracil may induce side effects such as nausea and vomiting. It can also produce adverse event on nervous system and visual changes which could interfere driving or the usage of heavy machinery.

Incompatibilities:

Flurac is incompatible with carboplatin, cisplatin, cytarabine, diazepam, doxorubicin, other anthracyclines and possibly methotrexate.

Formulated solutions are alkaline and it is recommended that admixture with acidic drugs or preparations should be avoided.

Instructions for Use:
Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C with Glucose 5% or Sodium Chloride 0.9% Injection B.P or Water for Injections B.P 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 taken place in controlled and validated aseptic conditions.
The product should be discarded if it appears brown or dark yellow in solution.
The remainder of solutions should be discarded after use: do not make up into multidose preparations.

Presentation:
For intravenous use. Flurac injection is available as follows:
5 ml containing 250 mg of Fluorouracil (50 mg/ml)
10 ml containing 500 mg of Fluorouracil (50 mg/ml)
20 ml vial containing 1 gm of Fluorouracil (50 mg/ml)
100 ml vial containing 5 gm of Fluorouracil (50 mg/ml)

Shelf life
Two years from the date of manufacturing.

Storage:
Store below 25°C. Protect from light.

Manufactured by:-
INTAS
INTAS PHARMACEUTICALS LTD.
Plot No: 457-458, Village-Matoda, Bavla road, Dist- Ahmedabad, Gujarat, India- 382 210.

Product Registration Holder:
Jetpharma Sdn Bhd
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