SUMMARY OF PRODUCT CHARACTERISTICS

1. **Name of the medicinal product**

(Fluorouracil Injection BP 250mg/5 ml)

2. **Pharmaceutical Form**

Pharmaceutical Dosage form of the product: Liquid Injection

Strength: 250mg/5ml

Route(s) of administration: Intravenous route of administration

3. Qualitative and Quantitative Composition

Urafil-50
(Fluorouracil Injection BP 250mg/5ml)

Composition
Label claim:
Each ml contains:

Fluorouracil BP	50 mg
(As Fluorouracil sodium)	
Water for injection	qs

4. Clinical Particulars

4.1 Therapeutic indications

Fluorouracil Injection is effective in the palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas.

4.2 Posology and method of administration

General instructions: Urafil Injection should be administered only intravenously, using care to avoid extravasation. No dilution is required.

All dosages are based on the patient's actual weight. However, the estimated lean body mass (dry weight) is used if the patient is obese or if there has been a spurious weight gain due to edema, ascites or other forms of abnormal fluid retention.

It is recommended that prior to treatment each patient be carefully evaluated in order to estimate as accurately as possible the optimum initial dosage of Urafil.

Dosage: Twelve mg/kg are given intravenously once daily for four successive days. The daily dose should not exceed 800 mg. *If no toxicity is observed,* 6 mg/kg are given on the 6th, 8th, 10th and 12th days *unless toxicity occurs.* No therapy is given on the 5th, 7th, 9th or 11th days. *Therapy is to be discontinued at the end of the 12th day, even if no toxicity has become apparent.*

Poor risk patients or those who are not in an adequate nutritional state should receive 6 mg/kg/day for three days. *If no toxicity is observed*, 3 mg/kg may be given on the 5th, 7th and 9th days *unless toxicity occurs.* No therapy is given on the 4th, 6th or 8th days. The daily dose should not exceed 400 mg.

A sequence of injections on either schedule constitutes a "course of therapy".

Maintenance Therapy: In instances where toxicity has not been a problem, it is recommended that therapy be continued using either of the following schedules:

1. Repeat dosage of first course every 30 days after the last day of the previous course of treatment.
2. When toxic signs resulting from the initial course of therapy have subsided, administer a maintenance dosage of 10 to 15 mg/kg/week as a single dose. Do not exceed 1 g per week.

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

4.3 Method of administration

Intravenous Route of Administration

4.4 Contraindications

Fluorouracil Injection therapy is contraindicated for patients in a poor nutritional state, those with depressed bone marrow function, those with potentially serious infections or those with a known hypersensitivity to Fluorouracil.

4.5 Special warning & precautions for use

It is recommended that URAFIL injection be given only by or under the supervision of a qualified physician who is experienced in cancer chemotherapy and who is well versed in the use of potent antimetabolites. Because of the possibility of severe toxic reactions, it is recommended that patients be hospitalized at least during the initial course of therapy.

The daily dose of urafil injection is not to exceed 800 mg.

Urafil should be used with extreme caution in poor risk patients with a history of high-dose pelvic irradiation or previous use of alkylating agents, those who have a widespread involvement of bone marrow by metastatic tumors or those with impaired hepatic or renal function.

Rarely, unexpected, severe toxicity (e.g., stomatitis, diarrhea, neutropenia and neurotoxicity) associated with 5-fluorouracil has been attributed to deficiency of dipyrimidine dehydrogenase activity. A few patients have been re-challenged with 5-fluorouracil and despite 5-fluorouracil dose lowering, toxicity recurred and progressed with worse morbidity. Absence of this catabolic enzyme appears to result in prolonged clearance of 5-fluorouracil.

Pregnancy–*Category D.*

Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil has been shown to be teratogenic in laboratory animals at dosages 1 to 3 times the maximum recommended human therapeutic dose.

There are no adequate and well-controlled studies with fluorouracil in pregnant women. While there is no evidence of teratogenicity in humans due to fluorouracil, it should be kept in mind that other drugs which inhibit DNA synthesis (*e.g.*, methotrexate and aminopterin) have been reported to be teratogenic in humans. Women of childbearing potential should be advised to avoid becoming pregnant. If the drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be told of the potential hazard to the fetus. Fluorouracil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

PRECAUTIONS

General – Fluorouracil is a highly toxic drug with a narrow margin of safety. Therefore, patients should be carefully supervised, since therapeutic response is unlikely to occur without some evidence of toxicity. Severe hematological toxicity, gastrointestinal hemorrhage and even death may result from the use of fluorouracil despite meticulous selection of patients and careful adjustment of dosage. Although severe toxicity is more likely in poor risk patients, fatalities may be encountered occasionally even in patients in relatively good condition.

Therapy is to be discontinued promptly whenever one of the following signs of toxicity appears:

- Stomatitis or esophagopharyngitis, at the first visible sign.
- Leukopenia (WBC under 3500), or a rapidly falling white blood count.
- Vomiting, intractable.
- Diarrhea, frequent bowel movements or watery stools.
- Gastrointestinal ulceration and bleeding.
- Thrombocytopenia, (platelets under 100,000).
- Hemorrhage from any site.

The administration of 5-fluorouracil has been associated with the occurrence of palmar-plantar erythrodysesthesia syndrome, also known as hand-foot syndrome. This syndrome has been characterized as a tingling sensation of hands and feet which may progress over the next few days to pain when holding objects or walking. The palms and soles become symmetrically swollen and erythematous with tenderness of the distal phalanges, possibly accompanied by desquamation. Interruption of therapy is followed by gradual resolution over 5 to 7 days.

Although pyridoxine has been reported to ameliorate the palmar-plantar erythrodysesthesia syndrome, its safety and effectiveness have not been established.

4.6 Interaction with other medicinal products and other forms of interactions

Leucovorin calcium may enhance the toxicity of fluorouracil.

4.7 Pregnancy and lactation

Teratogenic Effects - Pregnancy Category D.

Nonteratogenic Effects- Fluorouracil has not been studied in animals for its effects on peri- and postnatal development. However, fluorouracil has been shown to cross the placenta and enter into fetal circulation in the rat. Administration of fluorouracil has resulted in increased resorptions and embryolethality in rats. In monkeys, maternal doses higher than 40 mg/kg resulted in abortion of all embryos exposed to fluorouracil. Compounds which inhibit DNA, RNA and protein synthesis might be expected to have adverse effects on peri- and postnatal development.

Nursing Mothers:
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.

4.8 Effects on ability to drive and use machine
Not known.

4.9 Undesirable 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 fluorouracil. 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 reactions 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 followed by pain, erythema, and swelling.
- *Ophthalmic:* lachrymal duct stenosis, visual changes, lacrimation, photophobia.
- *Psychiatric:* disorientation, confusion, euphoria.
- *Miscellaneous:* thrombophlebitis, epistaxis, nail changes (including loss of nails).

4.10 Overdose

The possibility of overdosage with fluorouracil 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.

The acute intravenous toxicity of fluorouracil is as follows:

Species	**LD_{50}** (mg/kg ±S.E.)
Mouse	340 ± 17
Rat	165± 26
Rabbit	27 ± 5.1
Dog	31.5± 3.8

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Pyrimidine analogues

ATC code: L01BC02

Clinical Pharmacology:

The metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid. Thus, fluorouracil 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 fluorouracil 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 on those cells which grow more rapidly and which take up fluorouracil at a more rapid rate.

5.2 Pharmacokinetic Properties

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

7-20% of the parent drug is excreted unchanged in the urine in 6 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 fluorouracil results in degradation products (*e.g.*, CO_2, urea and α-fluoro-β-alanine) which are inactive. The inactive metabolites are excreted in the urine over the next 3 to 4 hours. When fluorouracil is labeled in the six carbon position, thus preventing the $_{14}C$ metabolism to CO_2, approximately 90% of the total radioactivity is excreted in the urine. When fluorouracil is labeled in the two carbon position, approximately 90% of the total radioactivity is excreted in expired CO_2. Ninety percent of the dose is accounted for during the first 24 hours following intravenous administration.

Following intravenous administration of fluorouracil, the mean half-life of elimination from plasma is approximately 16 minutes, with a range of 8 to 20 minutes, and is dose dependent. No intact drug can be detected in the plasma 3 hours after an intravenous injection.

5.3 Preclinical safety data

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6 Pharmaceutical Particulars

6.1 List of Excipients

Disodium Edetate BP
Tromethamine USP
Sodium Hydroxide BP
Water for Injection BP

6.2 Incompatibilities

None

6.3 Shelf life

The shelf life of the medicinal product as package for sale
24 Months

The shelf life after dilution or reconstitution according to directions
Not Applicable.

The shelf life after first opening the container
Not Applicable

6.4 Special precaution for storage

Store below 30^0C. Protect from light. Do not freeze.

6.5 Nature and contents of container

UNIT PACK: 5 ml amber coloured glass ampoule Type I and such 5 ampoules placed in a PVC clear tray. Such one tray is packed in a printed carton along with a pack insert.

7. Marketing Authorization Holder and Manufacturing site address

Name of Marketing Authorization Holder:
Khandelwal Laboratories Pvt. Ltd.

Address of manufacturing site:
B-1, Wagle Industrial Estate,
Thane - 400 604, India
Telephone: 00 91 22 25821793 / 0794
Fax: 00 91 22 25823837

8. Marketing Authorization Numbers

06362/06773/NMR/2018

9. Date of first authorization / renewal of the authorization

Jul 25, 2021

10. Date of revision of the text

Jul 25, 2021