Fluorouracil

Fucil®

50 mg/mL (500 mg/10 mL)
Solution for Injection/Infusion (I.V.)
Antineoplastic (Pyrimidine Analogue)

FORMULATION
Each mL solution for injection/infusion contains:
Fluorouracil, BP…….. 50 mg

PRODUCT DESCRIPTION
Fluorouracil (Fucil) is a sterile colorless or almost colorless solution contained and sealed in a Type 1 glass vial.

CLINICAL PHARMACOLOGY
Pharmacodynamics / Mechanism of Action
Fluorouracil (5-FU), a pyrimidine antagonist, is an antimetabolite antineoplastic agent. Its usefulness is based on uracil being utilized preferentially for nucleic acid biosynthesis in some tumors. Fluorouracil is metabolized in cells to 5-fluorouridine triphosphate (F-UTP), 2-deoxyfluorouridine monophosphate (Fd-UMP) and 2-deoxyfluoridine triphosphate (Fd-UTP) to concentrations that result in both DNA-directed and RNA-directed cytotoxicities. Fd-UMP is the intracellular cytotoxic form of fluorouracil. It competes with the natural substrate deoxyuridine monophosphate (d-UMP) for the catalytic site on thymidylate synthetase (a key enzyme in DNA synthesis), forming a covalent complex with the enzyme that is unable to undergo the normal catalytic reaction of converting d-UMP to deoxyuridine triphosphate (d-TMP). The presence of a reduced folate cofactor is required for tight binding of Fd-UMP to thymidylate synthetase. Leucovorin, which is metabolized to 5,10-methylene-tetrahydropteroylglutamine (a reduced folate), is able to modulate the antineoplastic effect of fluorouracil by promoting the formation and stabilization of the ternary complex formed between FdUMP and thymidylate synthetase. In this way, leucovorin produces a synergistic effect on fluorouracil therapy. In addition, F-UTP can be incorporated into RNA in place of uridine triphosphate (UTP), producing a fraudulent RNA and interfering with RNA processing and protein synthesis.

By interference with the formation of DNA and RNA, fluorouracil provokes unbalanced growth and death of cells. The effects of DNA and RNA deprivation are most marked on those cells which grow rapidly and those which take up fluorouracil rapidly.

Pharmacokinetics
The steady-state plasma concentrations of fluorouracil following bolus intravenous (IV) doses of 400 to 600 mg/m^2 (10 to 15 mg/kg body weight) range from 0.1 to 1 mM. Following continuous infusion of 1,100 mg/m^2/day, plasma concentrations of 0.5 to 2.5 µM are observed. Following IV administration of fluorouracil, no intact drug is detected in plasma after 3 hours. For bolus doses, fluorouracil plasma clearance is 0.5 to 1.4 L/min; clearance values are 10- to 60-fold higher following IV infusion. This non-linearity likely represents saturation of a metabolic or transport process at higher drug concentrations.

Distribution studies in humans and animals have suggested that the drug may possibly have some specificity against certain tumors in comparison with normal tissues. Fluorouracil crosses the placenta in rats. It is not known whether the drug is distributed into human milk. Despite its limited lipid solubility, the drug readily crosses the blood-brain barrier and distributes into cerebrospinal fluid (CSF) and brain tissue. CSF concentrations of about 7 µM are reached within 30 minutes after IV administration. Fluorouracil is distributed into tumors, intestinal mucosa, bone marrow, liver, and other tissues, with a volume of distribution ranging from 0.1 to 0.4 L/kg. Plasma protein binding of fluorouracil is 10%.

Following IV administration, the plasma elimination half-life averages about 16 minutes (range: 8 to 20 minutes) and is dose-dependent. The metabolism of fluorouracil occurs mainly in the liver and results in inactive degradation products. A large amount (60% to 80%) is excreted as respiratory carbon dioxide in 8 to 12 hours; urea and other metabolites are also excreted in the urine. Following a single IV dose of fluorouracil, approximately 15% of the dose is excreted in urine as intact drug within 6 hours; over 90% of this is excreted in the first hour.

INDICATIONS
Fluorouracil is used for the treatment of the following malignancies:
- **Carcinoma of the colon or rectum (Colorectal carcinoma)**
  - Alone or in combination with leucovorin for the treatment of advanced colorectal cancer
- **Breast cancer**
  - In combination chemotherapy as an adjunct to surgery in women with breast cancer

Fluorouracil has also shown activity in the following malignancies:
- Gastric cancer
- Primary hepatic cancer
- Pancreatic cancer
- Uterine (particularly cervical) cancer
- Ovarian cancer
- Bladder cancer

DOSAGE AND ADMINISTRATION
General Directions
Fluorouracil may be given by IV injection or IV infusion with the latter usually being preferred because of lesser toxicity. Care should be taken to avoid extravasation of the drug. The drug may be administered through a 25-gauge needle.

Fluorouracil (Fucil) does not contain any antimicrobial agent. When used for infusion, fluorouracil should be used immediately after dilution. The product is for single use in one patient only. Any residue should be discarded according to the guidelines for the disposal and handling of cytotoxic drugs (see **Special Handling Precautions**).

The dose of fluorouracil is based on the patient's actual weight unless the patient is obese or has fluid retention. In these latter instances, dose is based on ideal weight. Dosage can also be calculated according to body surface area. Dose must be based on the clinical and hematologic response and tolerance of the patient in order to obtain optimum therapeutic results with minimum adverse effects.

Clinicians should consult published protocols for the dosage and the method and sequence of administration of fluorouracil and other chemotherapeutic agents.

Usual Adult Dose:
As IV Injection
Initial course: Fluorouracil 12 mg/kg body weight once a day for 4 consecutive days
- If no toxic manifestations are observed, 6 mg/kg body weight is given on days 6, 8, 10, and 12 unless a toxic reaction occurs before then (no therapy is given on days 5, 7, 9, and 11).
- The daily dose should not exceed 800 mg in this regimen.
- Discontinue on day 12 even if no toxicity has become apparent.

An alternative regimen is 15 mg/kg body weight as a single IV injection once a week throughout the course.

As IV Infusion
Fluorouracil 15 mg/kg body weight (but not more than 1 g per infusion) diluted in 500 mL of 0.9% sodium chloride or 5% dextrose given once a day at a rate of 40 drops per minute over a period of 4 hours
- The infusion may be repeated on successive days until the first GI side effects (stomatitis and diarrhea) or hematological side effects (e.g., leukopenia or thrombocytopenia) appear or a total of 12 to 15 g has been given.
- Alternatively, the daily dose may be infused over 30 to 60 minutes or may be given as a continuous IV infusion over 24 hours.

As Intra-arterial Infusion
Fluorouracil 5 to 7.5 mg/kg body weight per day may be administered as a 24-hour intra-arterial continuous drip infusion.

Maintenance Therapy
- For patients in whom toxicity has not been a problem, the initial therapy should be repeated at intervals of 30 days after the last dose of the previous course.
- Alternatively, when toxicity from the initial course of therapy has subsided, a single weekly maintenance of 10 to 15 mg/kg may be administered; weekly maintenance dose should not exceed 1 g.

The dosage schedule to be used in repeated courses depends on the patient's reaction to the previous course and should be adjusted accordingly.

Combination Therapy with Leucovorin
Commonly employed regimen:
Fluorouracil by IV injection at a dose of 370 to 400 mg/m^2 (9 to 10 mg/kg body weight) for 5 days after administration of leucovorin 200 to 500 mg/m^2 (5 to 12 mg/kg body weight) for 5 days. Repeat course every 4 weeks.

The patient should be monitored for toxic signs. Drug therapy should be appropriately adjusted or discontinued if toxic signs such as GI bleeding manifest.

Recommendations for Poor Risk Patients

As IV Injection
Initial IV course of fluorouracil 240 mg/m^2 (6 mg/kg body weight) once a day for 3 days
- If no toxic manifestations are observed, fluorouracil 3 mg/kg body weight is given on days 5, 7 and 9 unless a toxic reaction occurs before then.
- The daily dose should not exceed 400 mg.
- Repeat course every 30 days.

As IV Infusion
Fluorouracil 240 mg/m^2 (6 mg/kg body weight) diluted in 500 mL of 0.9% sodium chloride or 5% dextrose given once a day over a period of 4 hours, until signs of toxicity are observed, usually within 8 to 15 days

Renal and Hepatic Impairment
Fluorouracil should be used with caution in patients with renal or hepatic impairment. Dose adjustment appropriate to the degree of impairment and to the reaction of the patient to the previous fluorouracil course should be taken into account.

Treatment with fluorouracil should be discontinued promptly whenever any of the following signs of toxicity appears:
- Stomatitis or esophagopharyngitis, at the first visible sign
- Leukocyte count falls below 3500/mm^3 or decreases rapidly
- Platelet count falls below 100,000/mm^3
- Granulocyte count falls below 1500/mm^3
- Intractable vomiting
- Diarrhea, frequent bowel movements or watery stools
- GI ulceration or bleeding
- Hemorrhage at any site
- Central or peripheral nervous system toxicity, including ataxia and tremor
- Cardiac toxicity

Dosage Reduction in Combination Therapy
When fluorouracil is combined with other antineoplastics of similar toxicity profile or with radiotherapy, the recommended dosage should be adjusted accordingly.

Incompatibilities
Preparations of fluorouracil are alkaline, and compatibility problems may be expected with acidic drugs and preparations, or those which are unstable in the presence of alkali. Fluorouracil is incompatible with carboplatin, cisplatin, cytarabine, diazepam, doxorubicin (and presumably other anthracyclines that are unstable at alkaline pH), leucovorin, methotrexate, filgrastim, gallium nitrate, metoclopramide, morphine, ondansetron, parenteral nutrition, and vinorelbine.

Special Handling Precautions

Preparation and Handling
- Fluorouracil should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Procedures for proper handling and disposal of anti-cancer drugs should be considered to minimize exposure to fluorouracil .
- Personnel should be trained in good techniques for reconstitution and handling.
- Pregnant staff should be excluded from working with fluorouracil .
- As for all antineoplastic agents, personnel handling fluorouracil should wear PVC gloves, safety glasses and protective clothing such as gowns and masks.
- Preparation of antineoplastics should be performed in a designated area, preferably a vertical laminar flow hood. The work surface should be covered with disposable plastic-backed absorbent paper.
- Luer-lock fitting syringes are recommended. Large bore needles are recommended to minimize pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.
- Fluorouracil is an irritant and highly toxic. Professional staff administering antineoplastic agents should exercise particular care to prevent spillage and contact with the drug.
- Avoid contact with skin and mucous membranes. If skin contact occurs, the area should be vigorously washed with soap and water. A bland cream may be used to treat the transient stinging of skin. In case of contact with eyes, irrigate immediately with water and contact a physician. If inhaled or ingested, seek immediate medical attention.
- As fluorouracil is frequently adsorbed by regular glass surfaces, silanized glass should be used when fluorouracil is given.
- Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.

Spillage/Contamination
- If spills occur, restrict access to the affected area.
- Wear two pairs of latex rubber gloves, mask, protective clothing, and safety glasses.
- Limit the spill by covering with a suitable material such as absorbent towels or adsorbent granules. Spills may also be treated with 5% sodium hypochlorite solution.
- Collect the absorbent/adsorbent and other debris from the spill and place in a leak-proof plastic container and label as cytotoxic waste.
- Clean the remaining spill area with ample amounts of water.

Disposal
- Adequate care and precaution should be taken in the disposal of items used to reconstitute fluorouracil.
- All materials that have come in contact with cytotoxic agents including needles, syringes, vials, and other materials which have come in contact with fluorouracil or articles associated with body waste should be segregated in a double sealed polyethylene bag and incinerated at 1000˚C or more for at least one second.
- If incineration is not possible, add household bleach (sodium hypochlorite solution) or 0.1 molar sodium hydroxide solution and place the sealed container in a landfill site.

CONTRAINDICATIONS
- Hypersensitivity to fluorouracil or any ingredient of the product
- Poor nutritional state
- Dihydropyrimidine dehydrogenase enzyme deficiency
- Depressed bone marrow function (generally a leukocyte count of ≤ 5000/mm^3 and/or a platelet count of ≤ 100,000/mm^3)
- Potentially serious infections
- Pregnant or breastfeeding women
- Management of non-malignant disease

WARNINGS AND PRECAUTIONS
Fluorouracil is a potent drug and should be prescribed only by physicians experienced with cancer chemotherapeutic drugs. Blood counts as well as renal and hepatic function tests should be performed regularly. Discontinue the drug if there is significant leukopenia (under 3500/mm^3) or granulocytopenia (under 1500/mm^3).

GI Effects
Anorexia and nausea are common adverse effects of fluorouracil , and vomiting occurs frequently. These reactions generally occur during the first week of therapy, can often be alleviated by antiemetics and generally subside within 2 or 3 days following therapy. Stomatitis is one of the most common and often the earliest sign of specific toxicity, appearing as early as the 4th day but more commonly on the 5th to 8th day of therapy. Diarrhea, which also occurs frequently, usually appears slightly later than stomatitis, but may occur more concurrently or even in the absence of stomatitis. Patients should be questioned and the mouth examined daily for early evidence of stomatitis. Appearance of stomatitis, as evidenced by either oral mucosal erythema or ulceration at the inner margin of the lips, or of esophagopharyngitis as evidenced by sore throat or dysphagia, necessitates cessation of therapy.

Hematologic Effects
Leukopenia (predominantly granulocytopenia), thrombocytopenia and anemia occur commonly with fluorouracil therapy; leukopenia usually occurs after an adequate course of fluorouracil therapy. The nadir of the white blood cell count usually occurs from the 9th to the 14th day after therapy is initiated but may occur as late as the 25th day after the first dose of fluorouracil; counts usually return to normal after about 30 days. Maximum thrombocytopenia has been reported to occur from the 7th to 17th day of therapy. Hematopoietic recovery is usually rapid and by the 13th day, blood cell counts have usually reached the normal range.

Leukocyte counts with differential should be made before each dose of fluorouracil is given. If the leukocyte count drops to < 2000/mm^3, the patient should be placed in protective isolation and appropriate measures taken for the prevention of infection. During maintenance therapy, counts before each course are sufficient.

Cardiac Effects
Fluorouracil should not be readministered after a documented cardiovascular reaction (arrhythmia, angina, ST segment changes) as there is a risk of sudden death. Fluorouracil should be used with caution in patients who experience chest pain during courses of treatment of those with heart disease.

Neurological Effects
In cases of severe neurological toxicity, continued treatment with fluorouracil is not recommended (see **Undesirable Effects**).

Carcinogenicity, Mutagenicity and Impairment of Fertility
Carcinogenicity: Long-term studies in animals to determine the carcinogenic potential of fluorouracil have not been performed; however, no evidence of carcinogenicity was observed in several animal studies following oral or IV administration of the drug for up to 1 year. *In vitro,* the drug has induced oncogenic transformation of fibroblasts from mouse embryo. The carcinogenic risk in humans is not known.

Mutagenicity: Fluorouracil has been shown to be mutagenic and clastogenic in a number of studies. In addition, the drug was mutagenic in the micronucleus test on mouse bone marrow cells and at very high concentrations, produced chromosomal breaks in hamster fibroblasts *in vitro*. Although the risk of mutagenesis in patients receiving 5-FU has not been evaluated, the possibility must be considered.

Impairment of Fertility: Fluorouracil has not been adequately studied in animals to determine the effects on fertility and general reproductive performance. Following intraperitoneal administration of 125 or 250 mg/kg in rats, chromosomal aberrations and changes in chromosomal organization of spermatogonia were induced; spermatogonial differentiation was also inhibited, resulting in transient infertility. In a strain of mouse that is insensitive to the induction of sperm head abnormalities after exposure to a number of chemical mutagens and carcinogens, no abnormalities were produced at oral dosages of up to 80 mg/kg daily. Following intraperitoneal administration at weekly doses of up to 25 or 50 mg/kg for 3 weeks during the preovulatory phases of oogenesis in female rats, the incidence of female matings was substantially reduced, development of preimplantation and postimplantation embryos was delayed, and the incidence of preimplantation lethality and chromosomal anomalies in the embryo was increased. In a limited study in rabbits, a single 25 mg/kg dose or daily doses of 5 mg/kg for 5 days had no effect on ovulation, appeared not to affect implantation, and had only a limited effect in producing zygote destruction. Drugs that inhibit DNA, RNA and protein synthesis such as fluorouracil may have adverse effects on gametogenesis.

Effects on the Ability to Drive and Use Machines
Fluorouracil may induce nausea and vomiting which could interfere with driving or the use of heavy machinery.

INTERACTIONS WITH OTHER MEDICAMENTS
Nucleoside Analogues (e.g., Brivudin and Sorivudine): The enzyme dihydropyrimidine dehydrogenase plays an important role in the degradation of fluorouracil. Nucleoside analogues can cause a sharp rise in plasma concentrations of fluorouracil and other fluoropyrimidines, with accompanying toxic reactions (e.g., severe leukopenia). A period of 4 weeks should elapse between the administration of fluorouracil and nucleoside analogues. Where applicable, determination of dihydropyrimidine dehydrogenase enzyme activity is indicated before starting treatment with 5-fluoropyrimidines.
Cimetidine: Pretreatment with cimetidine for 4 weeks may increase plasma concentrations of fluorouracil by 27%. The total body clearance was reduced by 28%. This may lead to increased plasma concentrations of fluorouracil .
Clozapine: Concomitant administration with fluorouracil should be avoided due to the increased risk of agranulocytosis
Interferon alfa-2b: Concomitant administration with fluorouracil has produced a marked increase in the initial plasma concentration of fluorouracil and a decrease in fluorouracil clearance
Leucovorin: Leucovorin and fluorouracil are routinely used together in the treatment of colorectal cancer due to their synergistic effect. Leucovorin is metabolized to a reduced folate co-factor that is necessary for maximal inhibition of thymidylate synthetase by Fd-UMP, the active metabolite of fluorouracil. Leucovorin enhances the DNA-directed toxicity of fluorouracil. This combination should be used with caution since leucovorin may exacerbate the GI toxicity of fluorouracil.
Levamisole: Combination therapy with fluorouracil has been associated with multifocal inflammation leukoencelopathy (MILE). Symptoms may include memory loss, confusion, paresthesia, muscle weakness, speech disturbances, coma, and seizures. The CSF may show mild pleocytosis, and computed tomography and magnetic resonance scans may show lesions in the white matter suggestive of demyelination. If this syndrome occurs, treatment should be discontinued immediately. The condition as at least partially reversible if fluorouracil and levamisole are discontinued and corticosteroids are given.
Methotrexate: Administration of methotrexate followed by fluorouracil leads to a synergistic interaction in the treatment of head and neck, breast and colorectal cancers. Biochemical modulation may occur through effects on RNA and DNA synthesis and enhancement of fluorouracil uptake. The importance of time interval between methotrexate and fluorouracil exposure in the treatment of metastatic colon cancer has been demonstrated. When these two agents are separated by 24 hours as compared with 1 hour, the response rate, time to progression and survival are significantly improved. However, different tumors may respond differently to changes in the time interval between methotrexate and fluorouracil. Fluorouracil preceded by methotrexate has been demonstrated to double the response rate to fluorouracil in metastatic colorectal cancer and produce survival benefits.
Metronidazole: Has been shown to reduce the clearance of fluorouracil and increase its toxicity in colorectal cancer patients
Mitomycin: Hemolytic-uremic syndrome has been reported to occur after long-term use of fluorouracil in combination with mitomycin.
Phenytoin: Patients taking phenytoin concomitantly with fluorouracil should undergo regular testing because of the possibility of elevated plasma levels of phenytoin resulting in symptoms of phenytoin toxicity.
Sorafenib: Has been reported to have variable effects on fluorouracil.
Warfarin: Marked elevations of prothrombin time and INR have been reported in a few patients stabilized on warfarin therapy following initiation of fluorouracil regimens.
Laboratory Test Alterations: Increase in or false positive results may be observed in tests for bilirubin (icteric index) and 5-hydroxyindole acetic acid in the urine. Fluorouracil could interfere with diagnostic tests of thyroid function by causing rises in total thyroxine and liothyronine due to increased globulin binding. Plasma albumin may be decreased because of drug-induced protein malabsorption.

STATEMENT ON USAGE FOR HIGH RISK GROUPS
Pregnancy and Lactation
Pregnancy Category D
Fluorouracil may cause fetal harm when administered to pregnant women. Although it is not known whether fluorouracil crosses the human placenta, it has been shown to cross the placenta and enter fetal circulation in rats. In monkeys, doses greater than 40 mg/kg resulted in abortion of all embryos exposed to the drug. Although there is no evidence to date of teratogenicity caused by fluorouracil in humans, other drugs that inhibit DNA synthesis (e.g., methotrexate) have been reported to be teratogenic in humans; in addition, drugs that inhibit DNA, RNA and protein synthesis such as fluorouracil may have adverse effects on perinatal and postnatal development. Fluorouracil should not be used in pregnancy.
Breastfeeding: It is not known whether fluorouracil is distributed into milk. Because fluorouracil inhibits DNA, RNA and protein synthesis, it is recommended that women do not breastfeed an infant while receiving the drug.
Geriatric
Fluorouracil 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 fluorouracil-based chemotherapy. These effects may be additive in older women. Close monitoring for multiple organ toxicities and vigorous supportive care from those with toxicity are necessary.
Pediatric
The safety and efficacy of fluorouracil in children have not been established.
Other Populations
Fluorouracil should be used with extreme caution and the initial dose may be reduced by one-third to one-half in the following patients:
- Undergone recent major surgery (within previous 30 days)
- Patients who have previously received high-dose irradiation therapy to bone marrow-bearing areas (pelvis, spine, ribs, etc.) or alkylating agents
- Impaired hepatic or renal function (see ***Dosage and Administration***)
- History of heart disease (see ***Warnings and Precautions***)
- Widespread metastatic involvement of the bone marrow
- Patients who are known or suspected to have a dihydropyrimidine dehydrogenase deficiency

UNDESIRABLE EFFECTS
Therapeutic response is unlikely to occur without some evidence of toxicity. The major toxic effects of fluorouracil are on the normal, rapidly proliferating tissues particularly of the bone marrow and lining of the GI tract. Toxicity is schedule-dependent: reducing the rate of injection to a slow infusion is associated with less hematological toxicity but does not decrease GI toxicity.

GI Effects: Anorexia, nausea and vomiting are common. Stomatitis and esophagopharyngitis are common signs of toxicity. Esophagitis, proctitis, GI ulceration and bleeding have been reported, and paralytic ileus occurred in two patients who received excessive doses.

Hematologic Effects: Leukopenia (predominantly granulocytopenia), thrombocytopenia and anemia are common. Pancytopenia, agranulocytosis and hemolytic anemia have also occurred. Leukopenia and thrombocytopenia may be less frequent during maintenance therapy.

Hypersensitivity Reactions: Allergic reactions including anaphylaxis, bronchospasm, urticaria, and pruritus have been reported. If anaphylactic shock occurs, the usual countermeasures should be employed.

Dermatologic Effects: Hair loss occurs frequently with fluorouracil therapy, and cosmetically significant alopecia has occurred in a substantial number of patients. Regrowth of hair has been reported even in patients receiving repeated courses of the drug. Partial loss of nails has occurred rarely, and diffuse melanosis of the nails has been reported. The most common type of dermatologic toxicity is a pruritic maculopapular rash which usually appears on the extremities and less frequently on the trunk. This rash is generally reversible and usually responsive to symptomatic treatment. An erythematous, desquamative rash involving the hands and feet has been reported in patients receiving fluorouracil (in some cases, prolonged infusions of high doses of the drug were administered). The rash may be accompanied by tingling of painful hands and feet, swollen palms and soles and phalangeal tenderness. These adverse effects, referred to as palmar-plantar erythrodysesthesia or hand-foot syndrome, may gradually disappear over 5 to 7 days after discontinuance of fluorouracil therapy.

Other dermatologic manifestations of fluorouracil toxicity have included dry skin and fissuring, diffuse erythema and scaling. Exposure to strong sunlight may intensify skin reactions to the drug. Seborrheic dermatitis has been reported in a few patients, but could not always be definitely attributed to fluorouracil. Recall phenomenon and photosensitivity manifested by erythema or increased pigmentation can occur with fluorouracil therapy.

Neurological Effects: Disorientation, confusion, euphoria, ataxia, dysarthria, nystagmus, headache, slurred speech, dizziness, unsteadiness, muscular weakness, vertigo, Parkinson-like symptoms, pyramid signs, aphasia, convulsions, coma, optic neuritis, peripheral neuropathy and acute cerebellar syndrome (which may persist after therapy is discontinued) have occurred rarely in patients receiving fluorouracil. Oculomotor disturbances have occurred occasionally. Extrapyramidal or cortical dysfunction (usually reversible) and isolated cases of leukoencelopathy have also been reported. These symptoms may persist after therapy is discontinued.

Ocular Effects: Conjunctivitis was commonly reported. Excessive lacrimation, dacryostenosis, visual changes, photophobia, diplopia, blepharitis, and ectropion have been uncommon. Lacrimal duct stenosis (canalicular fibrosis) associated with prolonged administration of fluorouracil has been rarely reported. This condition is reversible upon reduction or temporary cessation of fluorouracil therapy, but on occasion may necessitate surgical intervention.

Cardiovascular Effects: There have been reports of chest pain, tachycardia, breathlessness, ECG changes (ST segment changes), myocardial ischemia, angina (including Prinzmetal variant angina), precordial pain, cardiac arrhythmias, dilatative cardiomyopathy, ischemia and heart failure resulting rarely in death. Vasculitis, Raynaud's phenomenon and thromboembolism have been rarely reported.

Hepatic Effects: Hepatocellular damage and in very rare cases, fatal hepatic necrosis have been observed.

Infection: Due to immunosuppression, infections (sometimes serious), may develop in patients treated with fluorouracil. Sepsis was uncommon.

Others: Fever that occurred during the end of the 2nd week following the first dose of fluorouracil, and was usually not accompanied by demonstrable infection, has been reported. Epistaxis, thrombophlebitis, vein pigmentation, and dehydration have also been reported. Hyperuricemia was uncommon.

OVERDOSE AND TREATMENT
The main symptoms of overdose are nausea, vomiting, diarrhea, stomatitis, esophagopharyngitis, GI ulceration and bleeding, hemorrhage from any site, and bone marrow depression (including thrombocytopenia, leukopenia and agranulocytosis). No specific antidote exists. Patients who have been exposed to an overdose of fluorouracil should be monitored hematologically with regular white cell counts, differentials and platelet counts for at least 4 weeks. If abnormalities appear, appropriate symptomatic therapy should be utilized. Suitable countermeasures are withdrawal of medication or dose reduction and, depending on the symptoms, blood transfusions, leukocyte or platelet infusions or anti-infective therapy. Nausea, vomiting and diarrhea may be controlled by appropriate therapy.

STORAGE CONDITIONS
Store the vial in the original carton at temperatures not exceeding 30˚C. Do not refrigerate. Store in a dry place, protected from light. Keep out of the reach of children.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Fucil 50 mg/mL (500 mg/10 mL) Solution for injection/infusion (I.V.) - clear colorless glass vial (type 1) - 10 mL (Box of 1) - DR-XY41191
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