CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
40279

DRAFT FINAL PRINTED LABELING
CONTAINER AND CARTON LABEL

50 mg/mL, 20mL  Product Code: 101720
CONTAINER AND CARTON LABEL

50mg/mL, 10 mL  Product Code: 101710
Poor risk patients or those who are not in an adequate nutritional state (see CONTRAINDICATIONS and WARNINGS sections) should receive 6 mg/kg/day for 3 days. If no toxicity is observed, 3 mg/kg may be given on the 4th, 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 single dose, sip-top-rins, and the dosage should be adjusted accordingly. Some patients have received from 8 to 10 courses of treatment during periods which ranged from 12 to 60 months.

Procedures for proper handling and disposal of antineoplastic drugs should be considered. Several guidelines on this subject have been published. It is recommended that all of the procedures recommended in the guidelines are necessary or appropriate.

Note

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 it precipitates occur due to exposure to low temperatures, resuspend by heating to 40°F and shaking vigorously; allow to cool to body temperature before using.

HOW SUPPLIED:

Tablets RBC

101710 63328-117-10 50 mg/mL in 10 mL

101720 63328-117-20 50 mg/mL in 20 mL

Store at controlled room temperature 15°C - 30°C (59°F - 86°F). DO NOT FREEZE. PROTECT FROM LIGHT.

Rx only

REFERENCES:


4. National Study Commission on Cytotoxic Exposure. Recommendations for handling cytotoxic agents. Available from Louis F. Jeffrey, ScD Director of Pharmacy Services, Rhode Island Hospital, 565 Eddy St, Providence, Rhode Island 02902.


American Pharmaceutical Partners, Inc.

45648/issued: April 1998

FLUOROURACIL INJECTION, USP

WARNING

It is recommended that FLUOROURACIL 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 antineoplastics. Because of the possibility of severe toxic reactions, it is recommended that patients be hospitalized at least during the initial course of therapy.

DESCRIPTION:

Fluorouracil injection, USP, an antimetabolic antineoplastic, is a colorless to yellow aqueous sterile, nonpyrogenic injectable solution for intravenous administration. Each mL contains: 50 mg Fluorouracil; pH adjusted to approximately 9.2 with sodium hydroxide.

Chemically, fluorouracil, a fluorinated pyrimidine, is 5-fluoro-2-4 (1H) pyrimidinedione. It is a white to practically white crystalline powder which is sparingly soluble in water. The molecular weight of fluorouracil is 130.06 and the structural formula is:

\[
\text{C}_4\text{H}_7\text{FN}_2\text{O}_5
\]

CLINICAL PHARMACOLOGY:

There is evidence that the metabolism of fluorouracil in the anaerobic pathway blocks the methylation reaction of deoxyuridinic acid to thymidinic acid. In this manner, 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 to cell division and growth, the effect of fluorouracil may be to create a thymine deficiency which provides unbalanced growth and death of the cell. The effects of DNA and RNA deprivation are most marked on those cells rich in mitotic activity and which take up fluorouracil at a more rapid rate.

Following intravenous injection, fluorouracil distributes into tumors, internal 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.

Seven to 20 percent of the parent drug is excreted unchanged in the urine in 6 hours. of this, over 80% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver. The catechol metabolites of fluorouracil results in degradation products (e.g., CO₂, H₂O and 6-fluoro-2-aminouracil) which are toxic. The major 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 incorporation of CO₂, incorporation of CO₂, approximately 10% of the total radioactivity is excreted in the urine. When fluorouracil is labeled in the two carbon position, approximately 80% of the total radiotracer is excreted in the urine. The majority of this is excreted in the first 24 hours following intravenous administration.

Following intravenous administration of fluorouracil, the mean half-life of elimination from plasma is approximately 18 minutes, with a range of 9 to 30 minutes, and is dose dependent. No intact drug can be detected in the plasma 3 hours after an intravenous injection.

INDICATIONS AND USAGE:

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

CONTRAINDICATIONS:

Fluorouracil therapy is contraindicated for patients in a poor nutritional state who...
in transgenic infarction. However, in studies with a strain of mice which is sensitive to the induction of sperm head abnormalities after exposure to genotoxic agents, fluorouracil did not produce any abnormalities. In rats, 50 mg/kg/day in female rats, fluorouracil administered intravenously at weekly doses of 25 or 50 mg/kg for 7 weeks during the preimplantation phase of oogenesis, significantly reduced the incidence of female matings, delayed the development of pregnancy, and prevented implantation. When embryos were removed from the uteri of dams treated with fluorouracil, the incidence of pre-implantation lethality and induced chromosomal anomalies in these embryos. In a limited study in rabbits, a single 25 mg/kg dose of fluorouracil or 5 daily doses of 5 mg/kg produced no adverse effects on reproductive performance, fertility, pregnancy, or survival. In mice, the use of fluorouracil in doses of 5 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 reproductive performance, fertility, pregnancy, and survival.

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 when ever 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 paroxysmal-planar erythrocyte-including wheal 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 syndromes have been reported to exacerbate the paroxysmal-planar erythrocyte-including syndrome, its safety and effectiveness have not been established.

Information for Patients
Patients should be informed of expected toxic effects, particularly oral manifestations. Patients should be alerted to the possibility of alopecia as a result of therapy and should be informed that it is usually a transient effect.

Laboratory Tests
White blood counts with differential are recommended before each dose.

Drug Interactions
Leucovorin calcium may enhance the toxicity of fluorouracil.

Also see WARNINGS section.

Cardiovascular:

Infarction, pulmonary embolism, myocardial infarction, myocardial ischemia, angina.

Gastrointestinal:

Ulceration and bleeding.

Allergic Reactions:

Anaphylactic and generalized allergic reactions.

Neurologic:

Acute cerebellar syndrome (which may persist following discontinuation of treatment), hypertonus, headache.

Dermatologic:

Skin rash, flushing, photosensitivity, pruritus, manifested by erythema or increased pigmentation of the skin, ven pigmentation, palm-planar erythrocyte-including syndrome, manifested by tingling of the hands and feet followed by pain, erythema and swelling.

Ophthalmic:

Lacrimal duct stenosis, visual changes, lacrimation, photophobia.

Psychiatric:

Depression, confusion, euphoria.

Miscellaneous:

Thrombocytopenia, epistaxis, nail changes (including loss of nails).

OVERDOSAGE:

The possibility of overdosing 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), leucopenia and agranulocytosis. No specific antidotal therapy is available. Patients who have been exposed to an overdose of fluorouracil should be monitored hemato logically for at least four weeks. Should abnormalities appear, appropriate therapy should be utilized.

The acute intravenous toxicity of fluorouracil is as follows:

Species
LD₅₀ (mg/kg S.E.)
Mouse

10
as hand-foot syndrome. This syndrome has
been characterized as aching sensation of
hands and feet which may progress over the next
few days to pain when holding objects or walk-
ing. The palms and soles become symmetrically
ychawed and erythematous with tenderness of
the distal phalanges, possibly accompanied
by desquamation. Interruption of therapy is fol-
lowed by gradual resolution over 5 to 7 days.
Although pyridoxine has been reported to ame-
liorate the palmar-plantar erythrodysesthesia
syndrome, its safety and effectiveness have
not been established.

Information for Patients
Patients should be informed of expected toxic
effects, particularly oral manifestations. Patients
should be alerted to the possibility of alopecia
as a result of therapy and should be informed
that it is usually a transient effect.

Laboratory Tests
White blood counts with differential are rec-
ommended before each dose.

Drug Interactions
Lactation: Calcium may enhance the toxicity of
fluorouracil.

Also see WARNINGS section.

Cardiac, Pulmonary, Impairment of Fertility
Cardiac
Long-term studies in animals to evaluate the
carcinogenic potential of fluorouracil have not
been conducted. However, there was no evi-
dence of carcinogenicity in small groups of rats
given fluorouracil orally at doses of 0.1, 0.3,
1 or 3 mg per rat 5 days per week for 52 weeks,
followed by a 6-month observation period. Also,
in other studies, 33 mg/kg of fluorouracil was
administered intravenously to male rats once a
week for 52 weeks followed by observation for
the remainder of their lifetimes with no evidence
of carcinogenicity. Female mice were given 1 mg
of fluorouracil intravenously once a week for 18
weeks with no effect on the incidence of lung
adenocarcinomas. On the basis of the available data,
no evaluation can be made of the carcinogenic
risk of fluorouracil to humans.

Pulmonary
Oncogenic transformation of fibroblasts from
mouse embryo has been induced in vitro by flu-
orouracil, but the relationship between oncog-
enicity and mutagenicity is not clear. Fluorouracil
has been shown to be mutagenic to several strains of Salmonella typhimurium,
including TA 1535, TA 1537 and TA 1538, and
to Saccharomyces cerevisiae, although no evi-
dence of mutagenicity was found with Salmo-
rella typhimurium strains TA 92, TA 98 and
TA 100. In addition, a positive effect was
observed in the micronucleus test on bone
marrow cells of the mouse, and fluorouracil at
very high concentrations produced chromo-
osomal breaks in hamster fibroblasts in vitro.

Impairment of Fertility
Fluorouracil has not been adequately studied in
animals to permit an evaluation of its effects
on fertility and general reproductive perform-
ance. However, doses of 125 or 250 mg/kg,
administered intraperitoneally, have been shown
to induce chromosomal aberrations and
changes in chromosomal organization of sper-
matogonia in rats. Spermatogonial differentia-
tion was also inhibited by fluorouracil, resulting

OVERDOSAGE:
The possibility of overdosage with Fluorouracil
is unlikely in view of the mode of administration.
Nevertheless, the anticipated manifestations
would be nausea, vomiting, diarrhea, gas-
trintestinal ulceration and bleeding, bone mar-
row 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:

<table>
<thead>
<tr>
<th>Species</th>
<th>LD₅₀ (mg/kg ± S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>340 ± 17</td>
</tr>
<tr>
<td>Rat</td>
<td>165 ± 20</td>
</tr>
<tr>
<td>Rabbit</td>
<td>27 ± 5.1</td>
</tr>
<tr>
<td>Dog</td>
<td>31.5 ± 3.8</td>
</tr>
</tbody>
</table>

DOSAGE AND ADMINISTRATION:

General Instructions
Fluorouracil Injection, USP should be adminis-
tered only intravenously, using care to avoid
evacuation. 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 opti-


DOSAGE

12 mg/kg are given intravenously once daily for
4 successive days. The daily dose should not
exceed 800 mg/m². If no toxicity is observed,
mg/kg are given on the 8th, 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. (See
WARNINGS and PRECAUTIONS.)
take up fluorouracil at a more rapid rate.

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.

Seven to 30 percent of the parent drug is excreted unchanged in the urine in 6 hours; of this, over 50% is excreted in the first hour. The remaining percentage of the administered dose is metabolized, primarily in the liver. The catalytic metabolism of fluorouracil results in degradation products (e.g., CO₂, urea and 5-fluoro-2-deoxyribose) which are inactive. The inactive metabolites are excreted in the urine over the next 3 to 4 hours. When fluorouracil is labeled in the 3-carbon position, thus preventing the 14C metabolism to CO₂, 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 CO₂. 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.

INDICATIONS AND USAGE:
Fluorouracil is effective in the palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas.

CONTRAINdications:
Fluorouracil 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.

WARNINGS:
THE DAILY DOSE OF FLUOROURACIL IS NOT TO EXCEED 800 MG. IT IS RECOMMENDED THAT PATIENTS BE HOSPITALIZED DURING THEIR FIRST COURSE OF TREATMENT.

Fluorouracil 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 widespread involvement of bone marrow by metastatic tumor 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 dihydropyrimidine dehydrogenase activity. A few patients have been rechallenged with 5-fluorouracil and despite 5-fluorouracil dose lowering, toxicity recurred and progressed with worse morbidity. Absence of this catalytic enzyme appears to result in prolonged clearance of 5-fluorouracil.

Pregnancy:
Teratogenic Effects: Pregnancy Category D.
Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil has been shown to be teratogenic in laboratory animals. Fluorouracil exhibited maximum teratogenicity when given to mice as single