PRESCRIBING INFORMATION

ADRUCIL*

(fluorouracil injection USP)

50 mg/mL

Antineoplastic Agent

Pfizer Canada Inc
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Kirkland, Quebec H9J 2M5

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(fluorouracil injection USP)

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CAUTION: ADRUCIL SHOULD BE ADMINISTERED ONLY BY OR UNDER THE SUPERVISION OF A QUALIFIED PHYSICIAN WHO IS EXPERIENCED IN CANCER CHEMOTHERAPY AND THE USE OF POTENT ANTIMETABOLITES.

THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

The mechanism of action of ADRUCIL (Fluorouracil Injection) is mainly related to 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. Also, moderate inhibition of ribonucleic acid (RNA) and incorporation of fluorouracil into RNA have been observed. The predominant mechanism of antitumour action appears to be dependent, at least in part, on individual tumour intracellular metabolism.

The effects of DNA and RNA deprivation are most marked on those cells which grow rapidly and which take up fluorouracil at a more rapid pace. Inactive degradation products (e.g., CO_2, urea, α-fluoro-β-alanine) result from the extensive catabolic metabolism of fluorouracil.

Following intravenous injection, no intact drug can be detected in the plasma after three hours and 60-80% of the dose is excreted as respiratory CO_2 in 8-12 hours. Within six hours approximately 15% of the total drug administered is excreted unchanged in the urine with over 90% of this excretion occurring in the first hour.

INDICATIONS AND CLINICAL USE

ADRUCIL (Fluorouracil Injection) used alone is effective in the palliative management of patients with carcinoma of the colon, rectum, breast, stomach and pancreas.

Clinical studies support the efficacy of ADRUCIL used with other chemotherapeutic agents in patients with carcinoma of the breast, stomach and pancreas. Listed below are tumour types and drugs used concurrently with ADRUCIL.

Carcinoma of the breast: ADRUCIL with cyclophosphamide and ADRIAMYCIN® (doxorubicin). ADRUCIL with cyclophosphamide and PHARMORUBICIN® (epirubicin). ADRUCIL with cyclophosphamide and ADRIAMYCIN (doxorubicin), vincristine and prednisone.

Carcinoma of the stomach: ADRUCIL with ADRIAMYCIN (doxorubicin) and mitomycin-C or ADRUCIL with PHARMORUBICIN (epirubicin).

Carcinoma of the pancreas: ADRUCIL with ADRIAMYCIN (doxorubicin) and mitomycin-C. ADRUCIL with mitomycin-C and streptozotocin.

A number of other solid tumours have also shown some responsiveness to ADRUCIL alone or in combination with other drugs. These include the following:

Cancer of the urinary bladder: ADRUCIL alone. ADRUCIL with ADRIAMYCIN (doxorubicin). ADRUCIL with ADRIAMYCIN (doxorubicin) and cisplatin. ADRUCIL with ADRIAMYCIN (doxorubicin) and cyclophosphamide. ADRUCIL with methotrexate, cyclophosphamide and vincristine.

Cancer of the prostate: ADRUCIL alone. ADRUCIL with ADRIAMYCIN (doxorubicin) and cyclophosphamide.

Cancer of the head and neck: ADRUCIL with cisplatin.

Cancer of the ovary: ADRUCIL with hexamethylmelamine, cyclophosphamide and ADRIAMYCIN (doxorubicin).

No studies performed to date have shown malignant melanoma, kidney carcinoma, the leukemias and lymphomas, soft tissue and bone sarcomas, bronchogenic carcinoma, brain tumours and metastases to the central nervous system to be significantly responsive to ADRUCIL therapy.

CONTRAINDICATIONS

ADRUCIL (Fluorouracil Injection) therapy should not be started in patients with a poor nutritional state, depressed bone marrow function, or potentially serious infections.

WARNINGS

ADRUCIL (Fluorouracil Injection) should be used with extreme caution in poor risk patients with a history of high-dose pelvic irradiation, previous use of alkylating agents, or who have a widespread involvement of bone marrow by metastatic tumours, or impaired hepatic or renal function. Although severe toxicity and fatalities are more likely to occur in poor risk patients, these effects have occasionally been encountered in patients in relatively good condition. Severe hematologic toxicity, gastrointestinal haemorrhage, and even death may result from use of fluorouracil despite meticulous selection of patients and careful adjustment of dosage.

Usage in Pregnancy: Safe use of fluorouracil has not been established with respect to adverse effects on fetal development. Therefore, this drug should not be used during pregnancy, particularly in the first trimester, unless in the judgement of the physician 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.

PRECAUTIONS

ADRUCIL (Fluorouracil Injection) is a highly toxic drug with a narrow margin of safety and, thus, special attention must be given to its toxicity. Patients should be advised of expected toxic effects,

especially oral manifestations. White blood counts with differential and platelet counts are recommended before each dose. Knowledge of WBC nadir is necessary for eventual subsequent dosage adjustments.

Administration of ADRUCIL is to be discontinued promptly when one of the following signs of toxicity appear:

1. Stomatitis or esophagopharyngitis (at first visible sign)
2. Leukopenia (WBC<3500/mm^3) or rapidly falling white blood count.
3. Vomiting (intractable)
4. Diarrhea (frequent bowel movements or watery stools)
5. Gastrointestinal ulceration and bleeding
6. Thrombocytopenia (platelets < 100,000/mm^3)
7. Haemorrhage (from any site)

ADRUCIL should be resumed only when the patient has recovered from the above signs.

Drug Interaction: ADRUCIL with leucovorin, the latter usually given 24 hours after sequential administration of methotrexate and fluorouracil, may result in increased potency and toxicity.

ADRUCIL causes a change in the spectrophotometric spectrum of cytarabine, possibly reducing its effectiveness. ADRUCIL when mixed with methotrexate alters the spectra of both agents. ADRUCIL is physically incompatible with doxorubicin, epirubicin and with diazepam; a precipitate forms when ADRUCIL is mixed with these drugs. It is recommended that complete intravenous line flushing take place between injection of ADRUCIL and cytarabine, methotrexate, doxorubicin, epirubicin or diazepam.

ADVERSE REACTIONS

Stomatitis and esophagopharyngitis (which may lead to sloughing and ulceration), diarrhea, anorexia, nausea and emesis are common reactions to ADRUCIL (Fluorouracil Injection).

Myelosuppression almost uniformly accompanies a course of adequate therapy with fluorouracil. Low WBC counts are usually first observed between the 9th and 14th day after the first course of treatment

with the nadir occurring during the third week, although at times delayed for as long as 25 days. By the 30th day the count is usually within the normal range. Thrombocytopenia also may occur.

Alopecia and dermatitis are seen in a substantial number of cases and patients should be advised of this consequence of treatment. The alopecia is reversible. The dermatitis is often a pruritic maculopapular rash generally appearing on the extremities and less frequently on the trunk. It is usually reversible and responsive to symptomatic treatment. Palmar-plantar erythrodysesthesia has been reported in association with the continuous infusion of ADRUCIL. Dry skin and fissuring have also been noted.

Photosensitivity, as manifested by erythema or increased pigmentation of the skin, may occasionally occur. Also reported were photophobia, lacrimation, epistaxis, euphoria, acute cerebellar syndrome (which may persist following discontinuation of treatment) and nail changes including banding or loss of nails, and vein discolouration proximal to injection sites. Myocardial ischemia has also been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Signs and symptoms of overdosage include stomatitis, diarrhea, fever, infection and petechiae with bleeding. No antidotes are available; management of overdosage consists of supportive therapy including fluid replacement, antibiotics and platelet transfusions.

DOSAGE AND ADMINISTRATION

The recommended route of administration of ADRUCIL (Fluorouracil Injection) is by intravenous injection, using care to avoid extravasation. No dilution of ADRUCIL is required. Although ADRUCIL can be used orally, the product is not formulated for this clinical application.

It is recommended that all dosages be based on the patient's actual weight. However, 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, then the estimated lean body mass (dry weight) should be used.

Prior to treatment, it is recommended that each patient be carefully evaluated to accurately estimate the optimum initial dosage of ADRUCIL.

Initial Therapy (See Contraindications, Warnings and Precautions before prescribing). Patients should be hospitalized during the first course of therapy. Daily dosage generally should not exceed 800 mg.

1. In good risk patients a dose of 12 mg/kg (500 mg/m^2) is given daily for five days and repeated every twenty-eight days.
2. In poor risk patients a dose of 6 to 10 mg/kg (250 to 400 mg/m^2) is given daily for five days and repeated every twenty-eight days.
3. When used in combination with other chemotherapeutic agents various schedules may be used including a single dose per course, a dose on day one and day eight and daily for four or five days. The dose given varies, depending on the regimen used.

A sequence of one to five injections constitutes a “course of therapy”.

Therapy should be discontinued promptly when any of the signs of toxicity listed under PRECAUTIONS appears.

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:

A. Repeat dosage of the first course, beginning 28 days after the first day of the previous course of treatment.
A. Administer a maintenance dosage of 10-15 mg/kg/week. Reduced doses should be used for poor risk patients.

The dosage of drug 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 9-45 courses of treatment during periods which ranged from 12-60 months.

ADRUCIL (Fluorouracil Injection) should not be mixed with i.v. additives or other chemotherapeutic agents.

GUIDELINES FOR SAFE HANDLING AND DISPOSAL

Handling

1. Personnel involved in handling ADRUCIL solutions or in the clean-up of spillage and disposal operations should wear protective clothing, gloves, and glasses. If the solution contacts the skin, the area should be washed with soap and water immediately. If the solution accidentally contacts the eyes, irrigate immediately with water or saline.
2. Personnel regularly involved in the preparation and handling of antineoplastics should have blood examinations on a regular basis.

Disposal

1. All needles, syringes, vials and other materials which have come in contact with fluorouracil should be segregated in plastic bags, sealed and marked as hazardous waste. Incinerate at 1000°C or higher. Sealed containers may explode if a tight seal exists.
2. If incineration is not available, ADRUCIL may be detoxified by adding sodium hypochlorite solution (household bleach). Dispose of detoxified ADRUCIL solution in a safe manner.
3. Non-disposable equipment should be rinsed in sodium hypochlorite solution and then washed in soap and water.

Spillage

Deactivate with sodium hypochlorite solution and rinse well with water.

AVAILABILITY

ADRUCIL (Fluorouracil Injection) is supplied as a 50 mg/mL sterile, non-preserved solution. The pH of the solution is adjusted with sodium hydroxide and hydrochloric acid to a range of 8.6 to 9.4. The following vial sizes are available.

500 mg (10 mL) vials supplied in 10 vial cartons.

Pharmacy Bulk Vials:

2.5 g (50 mL) vials supplied in single vial cartons.

NOTE:

THE USE OF PHARMACY BULK VIALS IS RESTRICTED TO HOSPITALS WITH A RECOGNIZED INTRAVENOUS ADMIXTURE PROGRAM. THE PHARMACY BULK VIAL IS INTENDED FOR SINGLE PUNCTURE, MULTIPLE DISPENSING AND FOR INTRAVENOUS USE ONLY.

Entry into vial must be made with a suitable, sterile transfer or dispensing device. Multiple use of a syringe with needle is not recommended since it may cause leakage as well as it may increase the potential for microbial and particulate matter contamination.

In a suitable work area such as a laminar flow hood, swab the vial stopper with an antiseptic solution. Insert the device into the vial.

Withdraw contents of the vial into sterile syringes using strict aseptic techniques. Dispensing from the Pharmacy Bulk Vial should be completed within eight hours of the initial entry because of the potential for microbial contamination. Discard any unused portion. The contents of the syringes filled from the Pharmacy Bulk Vial should be used within 24 hours at room temperature from the time of the initial entry into the Pharmacy Bulk Vial.

STORAGE:

Store at controlled room temperature (15°-30°C) preferably below 25°C. Protect from freezing and from light.

Note: ADRUCIL solution may turn a very pale yellowish colour during storage. A highly coloured solution is evidence of degradation and its use is not recommended. If a precipitate occurs due to exposure at low temperatures, re-solubilize by heating to 60°C with vigorous shaking; allow to cool to body temperature before using.

Reviewed: June 2001