

PERCENT OF CLL PATIENTS REPORTING NON-HEMATOLOGIC ADVERSE EVENTS

ADVERSE EVENTS	MDAH (N=101)	SWOG (N=32)
ANY ADVERSE EVENT	88%	91%
BODY AS A WHOLE	72	84
FEVER	60	69
CHILLS	11	19
FATIGUE	10	38
INFECTION	33	44
PAIN	20	22
MALAISE	8	6
DIAPHORESIS	1	13
ALOPECIA	0	3
ANAPHYLAXIS	1	0
HEMORRHAGE	1	0
HYPERGLYCEMIA	1	6
DEHYDRATION	1	0
NEUROLOGICAL	21	69
WEAKNESS	9	65
PARESTHESIA	4	12
HEADACHE	3	0
VISUAL DISTURBANCE	3	15
HEARING LOSS	2	6
SLEEP DISORDER	1	3
DEPRESSION	1	0
CEREBELLAR SYNDROME	1	0
IMPAIRED MENTATION	1	0
PULMONARY	35	69
COUGH	10	44
PNEUMONIA	16	22
DYSPNEA	9	22
SINUSITIS	5	0
PHARYNGITIS	0	9
UPPER RESPIRATORY INFECTION	2	16
ALLERGIC PNEUMONITIS	0	6
EPISTAXIS	1	0
HEMOPTYSIS	1	6
BRONCHITIS	1	0
HYPOXIA	1	0
GASTROINTESTINAL	46	63
NAUSEA/VOMITING	36	31
DIARRHEA	15	13
ANOREXIA	7	34
STOMATITIS	9	0
GI BLEEDING	3	13
ESOPHAGITIS	3	0
MUCOSITIS	2	0
LIVER FAILURE	1	0
ABNORMAL LIVER FUNCTION TEST	1	3
CHOLELITHIASIS	0	3
CONSTIPATION	1	3
DYSPHAGIA	1	0
CUTANEOUS	17	18
RASH	15	15
PRURITUS	1	3
SEBORRHEA	1	0
GENITOURINARY	12	22
DYSURIA	4	3
URINARY INFECTION	2	15
HEMATURIA	2	3
RENAL FAILURE	1	0
ABNORMAL RENAL FUNCTION TEST	1	0
PROTEINURIA	1	0
HESITANCY	0	3
CARDIOVASCULAR	12	38
EDEMA	8	19
ANGINA	0	6
CONGESTIVE HEART FAILURE	0	3
ARRHYTHMIA	0	3
SUPRAVENTRICULAR TACHYCARDIA	0	3

PERCENT OF CLL PATIENTS REPORTING NON-HEMATOLOGIC ADVERSE EVENTS (continued)

ADVERSE EVENTS	MDAH (N=101)	SWOG (N=32)
MYOCARDIAL INFARCTION	0	3
DEEP VENOUS THROMBOSIS	1	3
PHLEBITIS	1	3
TRANSIENT ISCHEMIC ATTACK	1	0
ANEURYSM	1	0
CEREBROVASCULAR ACCIDENT	0	3
MUSCULOSKELETAL	7	16
MYALGIA	4	16
OSTEOPOROSIS	2	0
ARTHRALGIA	1	0
TUMOR LYSIS SYNDROME	1	0

More than 3,000 adult patients received fludarabine in studies of other leukemias, lymphomas, and other solid tumors. The spectrum of adverse effects reported in these studies was consistent with the data presented above.

OVERDOSAGE:

High doses of Fludarabine Phosphate Injection, USP (see **WARNINGS** section) have been associated with an irreversible central nervous system toxicity characterized by delayed blindness, coma, and death. High doses are also associated with severe thrombocytopenia and neutropenia due to bone marrow suppression. There is no known specific antidote for Fludarabine Phosphate Injection, USP overdose. Treatment consists of drug discontinuation and supportive therapy.

DOSAGE AND ADMINISTRATION:

Usual Dose

The recommended adult dose of Fludarabine Phosphate Injection, USP is 25 mg/m² administered intravenously over a period of approximately 30 minutes daily for five consecutive days. Each 5 day course of treatment should commence every 28 days. Dosage may be decreased or delayed based on evidence of hematologic or nonhematologic toxicity. Physicians should consider delaying or discontinuing the drug if neurotoxicity occurs.

A number of clinical settings may predispose to increased toxicity from Fludarabine Phosphate Injection, USP. These include advanced age, renal insufficiency, and bone marrow impairment. Such patients should be monitored closely for excessive toxicity and the dose modified accordingly.

The optimal duration of treatment has not been clearly established. It is recommended that three additional cycles of Fludarabine Phosphate Injection, USP be administered following the achievement of a maximal response and then the drug should be discontinued.

Renal Insufficiency

Adult patients with moderate impairment of renal function (creatinine clearance 30 to 70 mL/min/1.73 m²) should have a 20% dose reduction of Fludarabine Phosphate Injection, USP. Fludarabine Phosphate Injection, USP should not be administered to patients with severely impaired renal function (creatinine clearance less than 30 mL/min/1.73 m²).

Preparation of Solutions

Fludarabine Phosphate Injection, USP: Each mL contains 25 mg fludarabine phosphate, 25 mg mannitol, water for injection, q.s.; and sodium hydroxide to adjust the pH to 6.8. The pH range for the final product is 6.0 to 7.1. In clinical studies, the product has been diluted in 100 cc or 125 cc of 5% dextrose injection USP or 0.9% sodium chloride USP.

Fludarabine Phosphate Injection, USP contains no antimicrobial preservative and thus should be used within 8 hours of initial entry. Care must be taken to assure the sterility of prepared solutions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Handling and Disposal

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Procedures for proper handling and disposal should be considered. Consideration should

be given to handling and disposal according to guidelines issued for cytotoxic drugs. Several guidelines on this subject have been published.¹⁻⁸ There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Caution should be exercised in the handling of Fludarabine Phosphate Injection, USP. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution contacts the skin or mucous membranes, wash thoroughly with soap and water; rinse eyes thoroughly with plain water. Avoid exposure by inhalation or by direct contact of the skin or mucous membranes.

HOW SUPPLIED:

Fludarabine Phosphate Injection, USP is supplied as a clear, sterile solution. Each mL contains 25 mg of fludarabine phosphate, 25 mg of mannitol, water for injection, q.s.; and sodium hydroxide to adjust pH to 6.8. The pH range for the final product is 6.0 to 7.1.

Product No.	NDC No.	
109002	63323-192-02	Fludarabine Phosphate Injection, USP, 50 mg per 2 mL (25 mg per mL) in a 2 mL single dose vial, packaged individually.

REFRIGERATE AT: 2° to 8°C (36° to 46°F).

The container closure is not made with natural rubber latex.

REFERENCES:

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice. Pittsburgh, Pa: Oncology Nursing Society. 1999:32-41.
2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. Washington, DC: Division of Safety, Clinical Center Pharmacy Department and Cancer Nursing Services, National Institute of Health; 1992. US Department of Health and Human Services, Public Health Service Publication NIH 92-2621.
3. AMA Council on Scientific Affairs. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985;253:1590-1591.
4. National Study Commission on Cytotoxic Exposure – Recommendations for Handling Cytotoxic Agents. 1987. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.
5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia*. 1983;1:426-428.
6. Jones, R.B, Frank R, Mass T. Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. *CA Cancer Clin*. 1983; 33:258-263.
7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm*. 1990; 47:1033-1049.
8. Controlling Occupational Exposure to Hazardous Drugs (OSHA Work-Practice Guidelines). *Am J Health-Syst Pharm*. 1996; 53:1669-1685.



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