A correlation was noted between the degree of absolute granulocyte count nadir and increased area.

Fludarabine phosphate, USP, intended for intravenous administration. A loading dose of 8 mg/m²/day followed by a continuous infusion of 23.5 mg/m²/day for 5 days. The maximum allowed dose is 30 mg/m²/day. Fludarabine phosphate for injection is supplied as a lyophilized powder containing 10 mg of fludarabine phosphate per vial. The product is available as 30-mL and 60-mL vials.

Pulmonary System

Additional reports of cerebral hemorrhage though the frequency is not known.

Fludarabine phosphate was clastogenic in in vitro and in vivo tests (see Carcinogenesis, Mutagenesis, and Impairment of Fertility).

Bone Marrow Suppression

Monitoring of hematologic parameters should be carried out at baseline and during the course of treatment with fludarabine phosphate for injection. Hematologic compromise was the major dose-limiting toxicity observed in Phase I/II trials. In general, hematologic recovery was seen within about 14 days of completion of treatment. In patients with previously treated CLL, the nadir in absolute granulocyte count and platelet count was observed usually 4 to 8 weeks after the initiation of therapy. In newly treated patients, the nadir was generally reached early.

Male Fertility and Reproductive Outcomes

Males with female sexual partners of childbearing potential should use contraception during and for at least 6 months after the last dose of fludarabine phosphate for injection. Fludarabine phosphate for injection must be administered cautiously in patients with renal impairment (see Precautions). The cumulative incidence of decreased serum sperm count in men treated with fludarabine phosphate for injection was low (≤ 10%). After an infectious origin has been excluded, patients should be monitored closely for excessive toxicity and the dose modified accordingly.

Skin toxicity, consisting primarily of skin rashes, has been reported in patients treated with fludarabine phosphate for injection. Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms have been reported in patients who have received fludarabine phosphate for injection. It is important to note that these skin reactions have been reported in patients with a history of other skin conditions or those who have received other therapies. Fludarabine phosphate for injection is not recommended for the treatment of patients with ocular involvement.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Coma and death. Symptoms appeared from 21 to 60 days following the last dose. Thirteen of 133 adult CLL patients treated with fludarabine phosphate for injection in the two trials experienced Grade 4 infections. During fludarabine phosphate for injection treatment, neutrophil counts became increasingly abnormal in CLL patients with pre-existing cytopenias. Cumulative neutrophils inclusive of those with a history of concomitant or subsequent treatment with alkylating agents, carmustine, or cyclophosphamide.

The clinical laboratory values for fludarabine phosphate for injection are available from a published clinical trial. Fludarabine phosphate for injection is supplied as a lyophilized powder containing 10 mg of fludarabine phosphate per vial. The product is available as 30-mL and 60-mL vials. Fludarabine phosphate for injection must be administered cautiously in patients with renal impairment (see Precautions). Fludarabine phosphate for injection has been evaluated in 62 pediatric patients (median age 10, range 2 to 17 years) with previously untreated or previously treated, relapsed, or refractory CLL. The incidence of Grade 3 infections was higher in patients treated with fludarabine phosphate for injection at the recommended dose. In a clinical investigation using fludarabine phosphate for injection in combination with pentostatin, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate for injection in combination with pentostatin is not recommended.

Most common adverse events include fever, chills, asthenia, rash, nausea, and diarrhea. Other commonly reported events include malaise, mucositis and anorexia. Serious adverse events occurring in at least 1% of patients treated with fludarabine phosphate for injection include sepsis, neutropenia, neutropenic fever, febrile neutropenia, and infection.

Bone Marrow Suppression

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Fludarabine Phosphate for Injection, USP is supplied as follows:

NDC Fludarabine Phosphate for Injection, USP Package Factor 24201-237-01

50 mg Single-Dose Vial 1 vial per carton

Fludarabine Phosphate for Injection, USP is supplied as a white, lyophilized solid cake. Each vial contains 50 mg of fludarabine phosphate, 50 mg of mannitol, USP, and sodium hydroxide to adjust pH to 7.7. The pH range for the final product is 7.2 to 8.2.

Fludarabine Phosphate for Injection, USP is supplied in a clear glass single dose vial (6 mL capacity) and packaged individually.

Storage Conditions

Store refrigerated between 2° and 8°C (36° and 46°F).

Sterile, Nonpyrogenic, Preservative-free.

REFERENCES

1. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.