HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FLUDARABINE PHOSPHATE INJECTION safely and effectively. See full prescribing information for FLUDARABINE PHOSPHATE INJECTION.

FLUDARABINE PHOSPHATE injection, for intravenous use
Initial U.S. Approval: 1991

----------RECENT MAJOR CHANGES----------

Boxed Warning (removed)	11/2024
Indications and Usage (1)	11/2024
Dosage and Administration, Recommended Dosage (2.1)	11/2024
Warnings and Precautions (5)	11/2024

----------INDICATIONS AND USAGE----------

Fludarabine Phosphate Injection is a nucleoside metabolic inhibitor indicated:

- as a component of a combination regimen for the treatment of adults with B-cell chronic lymphocytic leukemia (CLL); (1)
- for the treatment of adults with B-cell CLL who have not responded to, or whose disease has progressed during treatment with at least one alkylating-agent containing regimen. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage is:
  - In Combination with Cyclophosphamide and Rituximab: The recommended dosage is 25 mg/m^2 administered intravenously over 30 minutes daily for the first three days (Days 1 to 3) of each 28-day cycle for 6 cycles in combination with cyclophosphamide 250 mg/m^2 administered intravenously daily for three days (Days 1 to 3), and rituximab 375 mg/m^2 administered intravenously on Day 1 of the first cycle, followed by rituximab 500 mg/m^2 on Day 1 of subsequent cycles. (2.1)
  - Single Agent: The recommended dosage is 25 mg/m^2 administered intravenously over approximately 30 minutes daily for five consecutive days (Days 1 to 5) of each 28-day cycle. (2.1)
- Renal impairment: Reduce the dosage for patients with creatinine clearance (CLcr) 30 to 79 mL/min. (2.2, 8.6)
- See the Full Prescribing Information for instructions for preparation and administration. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 50 mg/2 mL (25 mg/mL) (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

Neurological Toxicities: Coma, seizures, agitation and confusion can occur and are dose dependent. Monitor patients for signs and symptoms of neurologic toxicity. Consider delaying or discontinuing Fludarabine Phosphate Injection if neurotoxicity occurs. (5.1, 10)

Myelosuppression: Severe anemia, thrombocytopenia, neutropenia, or pancytopenia can occur and are dose dependent. Monitor blood counts before and during treatment. Consider dose delays, dose reductions, or permanent discontinuation if recovery has not occurred by the first day of the next scheduled cycle. (5.2, 10)

Autoimmune Cytopenias: Life-threatening and fatal autoimmune hemolytic anemia, autoimmune thrombocytopenia/ thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia can occur. Closely monitor patients for hemolysis and manage as clinically indicated. (5.3)

Transfusion-Associated Graft-Versus-Host Disease: Use only irradiated blood products for transfusions. (5.4)

Tumor Lysis Syndrome (TLS): Closely monitor patients at risk for TLS, consider appropriate prophylaxis including hydration, and manage as clinically indicated. (5.5)

Pulmonary Toxicity in Patients with CLL when Fludarabine Phosphate is Used with Pentostatin: Severe and sometimes fatal pulmonary toxicity when used concomitantly with pentostatin. Concomitant use is not recommended. (5.6, 7.1)

Vaccination: Avoid live attenuated vaccines during or after treatment with Fludarabine Phosphate Injection. (5.7)

Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception. (5.8, 8.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 20%) are myelosuppression (neutropenia, thrombocytopenia, or anemia), fever, infection, nausea and vomiting, weakness, and pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise not to breastfeed. (8.2)
- Infertility: May impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Fludarabine Phosphate Injection is indicated:

- as a component of a combination regimen for the treatment of adults with B-cell chronic lymphocytic leukemia (CLL);
- for the treatment of adults with B-cell CLL who have not responded to or whose disease has progressed during treatment with at least one alkylating-agent containing regimen.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

In Combination with Cyclophosphamide and Rituximab

The recommended dosage of Fludarabine Phosphate Injection is 25 mg/m^2 administered intravenously over 30 minutes daily for the first three days (Days 1 to 3) of each 28-day cycle for 6 cycles or until unacceptable toxicity or disease progression, in combination with cyclophosphamide 250 mg/m^2 administered intravenously daily for three days (Days 1 to 3), and rituximab 375 mg/m^2 administered intravenously on Day 1 of the first cycle, followed by rituximab 500 mg/m^2 on Day 1 of subsequent cycles.

Refer to the cyclophosphamide and rituximab prescribing information for additional dosing information as appropriate.

Single Agent

The recommended dosage of Fludarabine Phosphate Injection is 25 mg/m^2 administered intravenously over 30 minutes daily for five consecutive days (Days 1 to 5) of each 28-day cycle.

2.2 Recommended Dosage for Patients with Renal Impairment

Reduce the Fludarabine Phosphate Injection dosage for patients with renal impairment as shown in Table 1. Closely monitor patients with renal impairment for adverse reactions.

Table 1: Dosage Modifications for Renal Impairment

Creatinine Clearance (Estimated by Cockcroft-Gault equation)	**Recommended Dosage**
50 – 79 mL/min	20 mg/m^2
30 – 49 mL/min	15 mg/m^2
< 30 mL/min	A dosage has not been established.

2.3 Preparation and Administration

Fludarabine Phosphate Injection is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Dilute Fludarabine Phosphate Injection in 100 mL to 125 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Infuse diluted Fludarabine Phosphate Injection intravenously over 30 minutes.

Fludarabine Phosphate Injection contains no antimicrobial preservative. If not used immediately, discard the unused portion within 8 hours after opening the single-dose vial.

Do not mix Fludarabine Phosphate Injection with other drugs.

3 DOSAGE FORMS AND STRENGTHS

Injection: 50 mg/2 mL (25 mg/mL) fludarabine phosphate supplied as a a clear, colorless to almost colorless sterile solution in single-dose vials.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Neurologic Toxicities

Severe central nervous system (CNS) adverse reactions, including coma, seizures, agitation and confusion, can occur in patients treated with Fludarabine Phosphate Injection. CNS adverse reactions may occur either early or late after the initiation of Fludarabine Phosphate Injection (range 7 to 225 days).

CNS adverse reactions are dose dependent and occur at greater incidence and severity in patients treated at doses higher than the recommended dose of Fludarabine Phosphate Injection *[see Overdosage (10)].*

Monitor patients for signs and symptoms of neurologic toxicity during and after treatment with Fludarabine Phosphate Injection. Consider delaying or discontinuing Fludarabine Phosphate Injection if neurotoxicity occurs. Do not administer Fludarabine Phosphate Injection at doses higher than the recommended dose.

Advise patients that Fludarabine Phosphate Injection may reduce the ability to drive or use mechanical equipment, since fatigue, weakness, visual disturbances, confusion, agitation, or seizures may occur.

5.2 Myelosuppression

Fludarabine phosphate can cause severe and fatal myelosuppression, which may include neutropenia, thrombocytopenia, or anemia. Cases of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported.

The median time to nadir of counts was approximately 13 days (range, 3 to 25 days) for granulocytes and 16 days (range, 2 to 32 days) for platelets. The duration of the cytopenia in reported cases has ranged from approximately 2 months to approximately 1 year.

Monitor complete blood counts at baseline, prior to and during each treatment cycle, and as clinically needed. Consider dosage delays, dose reductions, or permanent discontinuation if recovery has not occurred by the first day of the next scheduled cycle.

5.3 Autoimmune Cytopenias

Life-threatening and fatal autoimmune hemolytic anemia, autoimmune thrombocytopenia/idiopathic thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia can occur in patients treated with fludarabine phosphate with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test.

The majority of patients rechallenged with fludarabine phosphate developed a recurrence in the hemolytic process. The mechanism(s) which predispose patients to the development of this complication has not been identified.

Closely monitor patients during treatment with Fludarabine Phosphate Injection for autoimmune cytopenias and manage as clinically indicated.

5.4 Transfusion Associated Graft-Versus-Host Disease

Transfusion-associated graft-versus-host disease has been observed after transfusion of non-irradiated blood in patients treated with fludarabine phosphate. Fatal outcome as a consequence of this disease has been reported. Therefore, to minimize the risk of transfusion-associated graft-versus-host disease, patients who require blood transfusion and who are undergoing, or who have received, treatment with Fludarabine Phosphate Injection should receive irradiated blood only.

5.5 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) can occur in patients treated with Fludarabine Phosphate Injection. TLS has been reported in patients with CLL who have large tumor burdens and can occur as early as the first week of treatment. Closely monitor patients at risk for TLS, consider appropriate prophylaxis including hydration, and manage as clinically indicated.

5.6 Pulmonary Toxicity in Patients with CLL When Fludarabine Phosphate is Used with Pentostatin

In clinical trials, patients experienced fatal pulmonary toxicity when treated with fludarabine phosphate and pentostatin for refractory CLL. Avoid concomitant use of Fludarabine Phosphate Injection with pentostatin *[see Drug Interactions (7.1)]*.

5.7 Vaccination

During and after treatment with Fludarabine Phosphate Injection, avoid vaccination with live vaccines.

5.8 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, Fludarabine Phosphate Injection can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of fludarabine phosphate to pregnant animals during organogenesis resulted in adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities at maternal doses below (rabbits) and above (rats) those in patients at the recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Fludarabine Phosphate Injection and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Fludarabine Phosphate Injection and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Neurologic Toxicities *[see Warnings and Precautions (5.1)]*
- Myelosuppression *[see Warnings and Precautions (5.2)]*
- Autoimmune Cytopenias *[see Warnings and Precautions (5.3)]*
- Transfusion Associated Graft-Versus-Host Disease *[see Warnings and Precautions (5.4)]*
- Tumor Lysis Syndrome *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

<u>B-cell Chronic Lymphocytic Leukemia</u>

Combination with Cyclophosphamide and Rituximab

The safety of Fludarabine Phosphate Injection for the treatment of adults with B-cell CLL as a component of a combination regimen was derived from the published literature *[see Clinical Studies (14)]*. The safety of Fludarabine Phosphate Injection for the treatment of adults with B-cell CLL as a component of a combination regimen was consistent with the known safety profile of fludarabine phosphate.

Single Agent

The safety of fludarabine phosphate was evaluated in two single-arm open-label studies (MDAH and SWOG) in adult patients (n=133) with CLL refractory to at least one prior alkylating-agent containing regimen *[see Clinical Studies (14)]*.

In these two clinical trials, 22% of the patients treated with fludarabine phosphate had fatal adverse reactions, with approximately 50% of these due to infection. Serious and fatal infections, including opportunistic and reactivation of latent viral infections such as Varicella-Zoster Virus (VZV; herpes zoster), Epstein-Barr Virus (EPV), and John Cunningham (JC) virus (progressive multifocal leukoencephalopathy) occurred in patients treated with fludarabine phosphate.

Hematologic adverse reactions, including neutropenia (Grade 4: 59%), thrombocytopenia (55%), and anemia (55%) occurred in a majority of the CLL patients treated with fludarabine phosphate.

The most common adverse reactions (≥ 20%) occurring in patients treated with fludarabine in the MDAH and SWOG trials (n=133) were myelosuppression (neutropenia, thrombocytopenia, or anemia), fever, infection, nausea and vomiting, weakness, and pain.

Table 2 summarizes the non-hematologic adverse reactions in the MDAH and SWOG studies.

Table 2: Non-Hematologic Adverse Reactions (≥ 5%) in CLL Patients Treated with Fludarabine in the MDAH and SWOG Studies

Adverse Reactions	**MDAH (N=101) %**	**SWOG (N=32) %**
General		
Fever	60	69
Pain	20	22
Fatigue	10	38
Chills	11	19
Malaise	8	6
Diaphoresis	1	13
Infection		
Infection	33	44
Pneumonia	16	22
Upper respiratory infection	2	16
Urinary infection	2	15
Sinusitis	5	0
Pharyngitis	0	9
Gastrointestinal		
Nausea/Vomiting	36	31
Anorexia	7	34
Diarrhea	15	13
Stomatitis	9	0
Gastrointestinal bleeding	3	13
Neurological		
Weakness	9	65
Paresthesia	4	12

Adverse Reactions	MDAH (N=101) %	SWOG (N=32) %
Visual disturbance	3	15
Hearing loss	2	6
Pulmonary		
Cough	10	44
Dyspnea	9	22
Allergic pneumonitis	0	6
Hemoptysis	1	6
Skin and Subcutaneous		
Rash	15	15
Cardiovascular		
Edema	8	19
Angina	0	6
Musculoskeletal		
Myalgia	4	16
Endocrine		
Hyperglycemia	1	6

Clinically relevant adverse reactions in < 5% of patients who received fludarabine phosphate included the following:

General: Headache, hemorrhage, tumor lysis syndrome (hyperuricemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, urate crystalluria, flank pain, renal failure)

Blood and Lymphatic: Bone marrow fibrosis, thrombocytopenia/ITP, Evans syndrome, acquired hemophilia

Cardiovascular: Congestive heart failure, arrhythmia, supraventricular tachycardia, myocardial infarction, transient ischemic attack, pericardial effusion

Gastrointestinal: Esophagitis, mucositis, constipation, dysphagia, pancreatic enzyme increase

Genitourinary: Dysuria, hematuria, renal failure, abnormal renal function test, proteinuria, hesitancy, hemorrhagic cystitis

Hepatobiliary: Liver failure, ALT/AST elevation, cholelithiasis

Immune System: Anaphylaxis

Infection: VZR (herpes zoster), EBV (lymphoproliferative disorders), JC virus (progressive multifocal leukoencephalopathy)

Musculoskeletal: Osteoporosis, arthralgia,

Neoplasms: tumor flare, skin cancer

Neurological: Sleep disorder, depression, cerebellar syndrome, impaired mentation, agitation, confusion, seizures, optic neuritis, optic neuropathy, blindness and coma, peripheral neuropathy, cerebral hemorrhage

Pulmonary: Epistaxis, bronchitis, hypoxia, interstitial pulmonary infiltrate

Renal &Urinary: Dehydration

Skin and Subcutaneous Tissue: Alopecia, pruritis, seborrhea; erythema multiforme, Steven-Johnson syndrome, toxic epidermal necrolysis, pemphigus (some fatal cases)

Vascular: Deep venous thrombosis, phlebitis, aneurysm, cerebrovascular accident

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of fludarabine phosphate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic: Bone marrow hypoplasia or aplasia resulting in pancytopenia (range: 2 months to 12 months after treatment initiation; some fatal); myelodysplastic syndrome and acute myeloid leukemia

Infection: Progressive multifocal leukoencephalopathy (range: 3 weeks to one year after treatment initiation; some fatal)

Pulmonary: Acute Respiratory Distress Syndrome (ARDS), respiratory distress, pulmonary hemorrhage, pulmonary fibrosis, pneumonitis, respiratory failure

7 DRUG INTERACTIONS

7.1 Pentostatin

Avoid use of Fludarabine Phosphate Injection in combination with pentostatin due to the risk of severe and fatal pulmonary toxicity *[see Warnings and Precautions (5.6)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1)]*, Fludarabine Phosphate Injection can cause fetal harm when administered to a pregnant woman. There are no available data on Fludarabine Phosphate Injection use in pregnant women to evaluate for a drug-associated risk. In animal reproduction studies, administration of fludarabine phosphate to pregnant animals during organogenesis resulted in adverse developmental outcomes, including embryo-fetal mortality and structural abnormalities at maternal doses below (rabbits) and above (rats) those in patients at the recommended human dose (see Data). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In rats, repeated intravenous doses of fludarabine phosphate at 2.4 times and 7.2 times the recommended human intravenous dose (25 mg/m^2) administered during organogenesis caused an increase in resorptions, skeletal and visceral malformations (cleft palate, exencephaly, and fetal vertebrae deformities) and decreased fetal body weights. Maternal toxicity was not apparent at 2.4 times the human intravenous dose, and was limited to slight body weight decreases at 7.2 times the human intravenous dose. In rabbits, repeated intravenous doses of fludarabine phosphate at 3.8 times the human intravenous dose administered during organogenesis increased embryo and fetal lethality as indicated by increased resorptions and a decrease in live fetuses. A significant increase in malformations including cleft palate, hydrocephaly, adactyly, brachydactyly, fusions of the digits, diaphragmatic hernia, heart/great vessel defects, and vertebrae/rib anomalies were seen in all dose levels (≥ 0.5 times the human intravenous dose).

8.2 Lactation

Risk Summary

There are no data on the presence of fludarabine phosphate or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with Fludarabine Phosphate Injection, and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

Fludarabine Phosphate Injection can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiation of Fludarabine Phosphate Injection *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise female patients of reproductive potential to use effective contraception during treatment with Fludarabine Phosphate Injection and for 6 months after the last dose.

Males

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with Fludarabine Phosphate Injection and for 3 months after the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Males

Based on findings in animals and humans, Fludarabine Phosphate Injection may impair male fertility. Fludarabine phosphate may damage testicular tissue and spermatozoa. Possible sperm DNA damage raises concerns about loss of fertility and genetic abnormalities in fetuses. The reversibility of this effect is unknown *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of Fludarabine Phosphate Injection have not been established in pediatric patients.

Safety and effectiveness were assessed, but not established for Fludarabine Phosphate Injection in pediatric patients 1 year to < 17 years with refractory acute leukemia or solid tumors. No new safety signals were observed in pediatric patients across these studies.

8.5 Geriatric Use

Among patients with CLL evaluated in two randomized active-controlled trials treated with fludarabine, cyclophosphamide, and rituximab, 36% were 65 years of age or older; of these, 15% were 70 years of age or older. The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving fludarabine in combination with cyclophosphamide and rituximab who were 70 years or older compared to younger patients for neutropenia, febrile neutropenia, anemia, thrombocytopenia, pancytopenia, and infections.

Clinical studies of fludarabine as a single agent for patients with B-cell CLL did not include a sufficient numbers of younger adults to determine if patients with B-cell CLL who are 65 years of age and older respond differently from younger adults.

8.6 Renal Impairment

Reduce the dosage in patients with CLcr 30 to 79 mL/min. A dosage has not been established for patients with severe renal impairment (CLcr < 30 mL/min) *[see Dosage and Administration (2.2)]*.

The total body clearance of 2-fluoro-ara-A is correlated with the creatinine clearance *[see Clinical Pharmacology (12.3)];* however, the effect of varying degrees of renal impairment on the pharmacokinetics of this metabolite has not been fully characterized.

10 OVERDOSAGE

Severe myelosuppression, including thrombocytopenia, neutropenia, anemia, and pancytopenia has occurred in patients treated with doses that exceed the recommended dosage of Fludarabine Phosphate Injection *[see Warnings and Precautions (5.3)].*

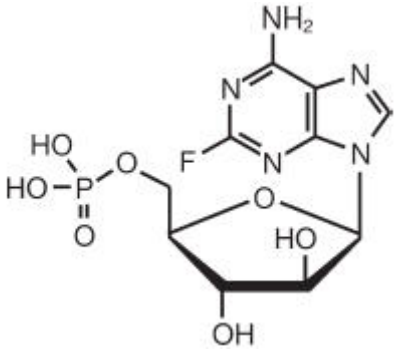
Severe, irreversible, central nervous system effects including blindness, coma, and death have occurred in patients treated at doses approximately four times greater (96 mg/m^2/day for 5 to 7 days) than the recommended dose for fludarabine phosphate *[see Warnings and Precautions (5.4)].*

There is no known specific antidote for fludarabine phosphate overdosage. Treatment consists of drug discontinuation and supportive therapy.

11 DESCRIPTION

Fludarabine Phosphate Injection contains fludarabine phosphate, a nucleoside metabolic inhibitor.

The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono-β-D-arabinofuranosyl)(2-fluoro-ara-AMP). The molecular formula of fludarabine phosphate is $C_{10}H_{13}FN_5O_7P$ (MW 365.2) and has the following chemical structure:



Each mL contains 25 mg of the active ingredient fludarabine phosphate (equivalent to 19.5 mg Fludarabine), 1.78 mg disodium phosphate dihydrate, water for injection and sodium hydroxide to adjust pH to 7.5. The pH range for the final product is 7.3 to 7.7. Fludarabine Phosphate Injection is a sterile solution intended for intravenous administration.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fludarabine phosphate is rapidly converted to active 2-fluoro-ara-ATP *[see Clinical Pharmacology (12.3)]*, which appears to inhibit DNA synthesis through inhibition of DNA polymerase alpha, ribonucleotide reductase and DNA primase.

12.2 Pharmacodynamics

The degree of absolute granulocyte count nadir is correlated with increased area under the concentration x time curve (AUC); however, the exposure-response relationship and time-course of pharmacodynamic response of fludarabine have not been fully characterized.

12.3 Pharmacokinetics

Fludarabine phosphate is a prodrug. It is rapidly converted to its active metabolite, 2-fluoro-ara-A which is the focus of the pharmacokinetic characterization. 2-fluoro-ara-A plasma trough concentration accumulated 2-fold.

Distribution

Plasma protein binding ranged between 19% and 29% in vitro.

Elimination

The terminal half-life of 2-fluoro-ara-A was approximately 20 hours. The total body clearance of 2-fluoro-ara-A correlated with the creatinine clearance. Renal clearance represents approximately 40% of the total body clearance.

Metabolism

Fludarabine phosphate is dephosphorylated to 2-fluoro-ara-A and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal carcinogenicity studies with fludarabine have been conducted.

Fludarabine phosphate was clastogenic in vitro to Chinese hamster ovary cells (chromosome aberrations in the presence of metabolic activation) and induced sister chromatid exchanges both with and without metabolic activation. In addition, fludarabine phosphate was clastogenic in vivo (mouse micronucleus assay) but was not mutagenic to germ cells (dominant lethal test in male mice). Fludarabine phosphate was not mutagenic to bacteria (Ames test) or mammalian cells (HGRPT assay in Chinese hamster ovary cells) either in the presence or absence of metabolic activation.

Studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male reproductive system. Observations consisted of a decrease in mean testicular weights in mice and rats with a trend toward decreased testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs.

14 CLINICAL STUDIES

B-cell Chronic Lymphocytic Leukemia

In Combination with Cyclophosphamide and Rituximab

The efficacy of Fludarabine Phosphate Injection for treatment of adults with B-cell CLL as a component of a combination regimen was derived from studies of fludarabine phosphate in the published literature. Fludarabine phosphate as a component of a combination regimen was evaluated in two randomized clinical trials (NCT00090051 and NCT00281918). In both trials, the major efficacy outcome measure was progression-free survival.

Single Agent

The efficacy of fludarabine phosphate was evaluated in two single-arm open-label studies in adult patients with CLL refractory to at least one prior alkylating-agent containing regimen.

The first study (MDAH) included 48 patients treated with a dose of 22 to 40 mg/m^2 for 5 days every 28 days daily (0.9 – 1.6 times the recommended dose). The second study (SWOG) included 31 patients treated with a dose of 15 to 25 mg/m^2 daily for 5 days every 28 days daily (0.6 – 1.0 times the recommended dose).

Patients in the SWOG trial had a median age of 63 years and a baseline median performance status of 1.

The overall objective response rates were 48% and 32% in the MDAH and SWOG studies, respectively. The complete response rate in both studies was 13%; the partial response rate was 35% in the MDAH study and 19% in the SWOG study. These response rates were obtained using standardized response criteria developed by the National Cancer Institute CLL Working Group.

The median time to response in the MDAH and SWOG studies was 7 weeks (range of 1 to 68 weeks) and 21 weeks (range of 1 to 53 weeks), respectively. The median duration of disease control was 91 weeks (MDAH)

and 65 weeks (SWOG). The median survival of all refractory CLL patients treated with fludarabine phosphate was 43 weeks and 52 weeks in the MDAH and SWOG studies, respectively.

Rai stage improved to Stage II or better in 7 of 12 MDAH responders (58%) and in 5 of 7 SWOG responders (71%) who were Stage III or IV at baseline. In the combined studies, mean hemoglobin concentration improved from 9.0 g/dL at baseline to 11.8 g/dL at the time of response in a subgroup of anemic patients. Similarly, average platelet count improved from 63,500/mm^3 to 103,300/mm^3 at the time of response in a subgroup of patients who were thrombocytopenic at baseline.

15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. https://www.osha.gov/hazardous-drugs

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Fludarabine Phosphate Injection is supplied as a clear, colorless to almost colorless sterile solution in a single-dose vial containing 50 mg/2 mL (25 mg/mL) of fludarabine phosphate.

NDC 66758-046-01 one carton containing 1 vial of Fludarabine Phosphate Injection.

Storage
Store in a refrigerator between 2° and 8°C (36° to 46°F).

Handling and Disposal
Fludarabine Phosphate Injection is a hazardous drug. Follow applicable special handling and disposal procedures.[1]
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.

17 PATIENT COUNSELING INFORMATION

Neurologic Toxicities
Inform patients that Fludarabine Phosphate Injection can cause severe CNS adverse reactions, including coma, seizures, agitation, and confusion. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider immediately if they experience signs or symptoms of CNS adverse reactions *[see Warnings and Precautions (5.1)]*.

Myelosuppression
Inform patients Fludarabine Phosphate Injection can cause a decrease in white blood cells, platelets, and red blood cells, and the need for frequent monitoring of blood counts. Advise patients to report shortness of breath, significant fatigue, bleeding, fever, or other signs of infection *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Autoimmune Cytopenias
Inform patients that Fludarabine Phosphate Injection can cause autoimmune hemolytic anemia, autoimmune thrombocytopenia/ITP, Evans syndrome, and acquired hemophilia. Advise patients to seek immediate medical attention if any signs or symptoms of autoimmune cytopenias occur *[see Warnings and Precautions (5.3)]*.

Tumor Lysis Syndrome

Inform patients about the risk of and the signs and symptoms of tumor lysis syndrome. Advise patients to notify their healthcare provider if they experience these symptoms *[see Warnings and Precautions (5.5)]*.

Vaccination

Advise patients they should avoid vaccinations with live vaccines during and after treatment *[see Warnings and Precautions (5.7)]*.

Nausea and Vomiting

Advise patients that Fludarabine Phosphate Injection may cause nausea and/or vomiting. Inform patients to report nausea and vomiting so that symptomatic treatment may be provided when this occurs *[see Adverse Reactions (6.1)]*.

Rash

Advise patients that a rash or itching may occur during treatment with Fludarabine Phosphate Injection. Advise patients to immediately report severe or worsening rash or itching *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise female patients to contact their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.8), Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception during treatment with Fludarabine Phosphate Injection and for 6 months after the last dose *[see Use in Specific Populations (8.3)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Fludarabine Phosphate Injection and for 3 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment and for 1 week after the last dose of Fludarabine Phosphate Injection *[see Use in Specific Populations (8.2)]*.

Infertility

Advise males of reproductive potential that Fludarabine Phosphate Injection may impair fertility *[see Use in Specific Populations (8.3)]*.

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