INDICATIONS AND USAGE

Fludarabine Phosphate Injection is indicated in combination with pentostatin for the treatment of patients with CLL (chronic lymphocytic leukemia) who have received at least one prior therapy and have evidence of disease progression or have relapsed. It is also indicated for palliative treatment of patients with CLL who have not responded to standard therapy with at least one prior therapy.

WARNINGS AND PRECAUTIONS

1. Indication

Fludarabine Phosphate Injection is indicated for the initial line therapy, in patients with sufficient bone marrow reserves.

2.2 Renal Impairment

Fludarabine is an alkylating agent or in whom the disease progressed during or after standard therapy. Fludarabine is indicated for the initial line therapy.

3. Use of Infusion Solutions

The recommended adult dose of Fludarabine Phosphate Injection contains 7.8 mg/mL. The solution is colorless, sterile solution intended for intravenous administration.

4. CONTRAINDICATIONS

Fludarabine Phosphate Injection is contraindicated in patients with severe renal impairment.

5. ADVERSE REACTIONS

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is a potential complication and may be particularly serious in patients at high risk for TLS.

5.6 Pulmonary Toxicity

Fatal pulmonary toxicity has been reported with the use of Fludarabine Phosphate Injection. Therefore, the use of Fludarabine Phosphate Injection should be evaluated and reported to occur after one or more cycles of therapy.

6. ADVERSE REACTIONS

The most common adverse reactions include hematologic and immune system effects. These effects may include increased fatigue, nausea, vomiting, and fever.

7. DRUG INTERACTIONS

7.2 Laboratory Tests

Drug-related effects on laboratory tests may include changes in hematologic, liver, and renal function.

8. USE IN SPECIFIC POPULATIONS

8.2 Pregnancy

Fludarabine Phosphate Injection contains folic acid and may cause fetal harm when administered to a pregnant woman. Women of childbearing potential must be placed on a contraceptive program during and for at least 30 days following therapy.

9. PATIENT EDUCATION

Patients should be instructed to report any symptoms of autoimmune hemolytic anemia, including fever, chills, shortness of breath, cough, and chest pain.

10. DESCRIPTION

Fludarabine Phosphate Injection is a colorless, sterile solution intended for intravenous administration.

11. CLINICAL STUDIES

Clinical trials have demonstrated the efficacy of Fludarabine Phosphate Injection in the treatment of CLL.

12. CLINICAL PHARMACOLOGY

Fludarabine Phosphate Injection is a purine nucleoside analog that inhibits DNA synthesis and is metabolized by deamination to yield a triphosphate that inhibits DNA polymerase.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Fludarabine Phosphate Injection was tested in nonclinical studies in animals and has been shown to be teratogenic and tumorogenic.

14. CLINICAL STUDIES

Clinical trials have demonstrated the efficacy of Fludarabine Phosphate Injection in the treatment of CLL.

15. DOSAGE AND ADMINISTRATION

The recommended adult dose of Fludarabine Phosphate Injection is 96 mg/m2/day for 5 to 7 days. This dose is administered in a single daily intravenous infusion.

16. HOW SUPPLIED

Fludarabine Phosphate Injection is available in vials containing 15 mL. Each mL of solution contains 7.8 mg/mL of Fludarabine Phosphate.

17. PATIENT INFORMATION

Patients should be instructed to report any symptoms of autoimmune hemolytic anemia, including fever, chills, shortness of breath, cough, and chest pain.

18. CLINICAL PHARMACOLOGY

Fludarabine Phosphate Injection is a purine nucleoside analog that inhibits DNA synthesis and is metabolized by deamination to yield a triphosphate that inhibits DNA polymerase.

19. CLINICAL STUDIES

Clinical trials have demonstrated the efficacy of Fludarabine Phosphate Injection in the treatment of CLL.

20. NONCLINICAL TOXICOLOGY

17.2 Laboratory Tests

Drug-related effects on laboratory tests may include changes in hematologic, liver, and renal function.

21. CLINICAL STUDIES

Clinical trials have demonstrated the efficacy of Fludarabine Phosphate Injection in the treatment of CLL.

22. DOSAGE AND ADMINISTRATION

The recommended adult dose of Fludarabine Phosphate Injection is 96 mg/m2/day for 5 to 7 days. This dose is administered in a single daily intravenous infusion.

23. HOW SUPPLIED

Fludarabine Phosphate Injection is available in vials containing 15 mL. Each mL of solution contains 7.8 mg/mL of Fludarabine Phosphate.

24. PATIENT INFORMATION

Patients should be instructed to report any symptoms of autoimmune hemolytic anemia, including fever, chills, shortness of breath, cough, and chest pain.
1. Introduction

Fludarabine phosphate is a purine analog for the treatment of chronic lymphocytic leukemia (CLL). It is a water-soluble prodrug that is converted to its active metabolite, 2-fluoro-ara-A, which is a potent DNA alkylating agent. Fludarabine phosphate is approved for the treatment of patients with CLL who have received at least one prior therapy and for the treatment of patients with Stage II or higher Rai stage disease. Fludarabine phosphate is also approved for the treatment of patients with non-Hodgkin's lymphoma (NHL) who have failed initial therapy and for the treatment of patients with hairy cell leukemia (HCL) who have failed initial therapy.

2. Use in Specific Populations

2.1 Pregnancy

Fludarabine phosphate is a Pregnancy Category D drug. It is not known whether fludarabine phosphate can cause fetal harm when administered to pregnant women. There are no adequate and well-controlled studies in pregnant women. If fludarabine phosphate is given to a pregnant woman, it should be administered only if the potential benefit justifies the potential risk to the fetus. Fludarabine phosphate is not recommended for use during pregnancy.

2.2 Nursing Mothers

It is not known whether fludarabine phosphate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fludarabine phosphate is administered to a nursing woman.

3. Nonclinical Toxicology

3.1 Acute Toxicity

In a 30-day dermal toxicity study in the mouse, the median LD50 (oral) was greater than 5000 mg/kg, and the median LD50 (intraperitoneal) was greater than 1400 mg/kg. In a 14-day dermal toxicity study in the rat, the median LD50 (oral) was greater than 5000 mg/kg, and the median LD50 (intraperitoneal) was greater than 1400 mg/kg.

3.2 Reproduction

There are no adequate and well-controlled studies in humans. In rats exposed to fludarabine phosphate during organogenesis, maternal toxicity was observed at doses of 30 and 60 mg/kg, and fetal toxicity was observed at doses of 60 and 120 mg/kg. These effects were not observed at doses of 15 mg/kg or less. There were no effects on reproductive performance in rats exposed to fludarabine phosphate prior to mating.

3.3 Carcinogenicity

Fludarabine phosphate was not mutagenic in the Ames test or in the mouse micronucleus test. Fludarabine phosphate was clastogenic in the mouse bone marrow micronucleus test after in vivo treatment, and may be mutagenic in the germ line of female mice. Fludarabine phosphate was not carcinogenic in long-term studies in mice and rats.

3.4 Skin and Eye Irritation

Fludarabine phosphate was not irritating to the skin or eyes in rabbit skin and eye irritation tests.

4. Animal Data

Fludarabine phosphate was evaluated in animal studies, including 21-day survival studies in mice and rats, and 15-week survival studies in mice. The drug was generally well-tolerated in these studies, with no apparent treatment-related mortalities.

5. Clinical Pharmacology

5.1 Pharmacokinetics

The pharmacokinetics of fludarabine phosphate have been studied in adult patients with CLL. The median terminal half-life of fludarabine phosphate was 7.2 hours, and the median area under the plasma concentration-time curve (AUC) was 774.4 ng•h/mL. The median clearance of fludarabine phosphate was 140 mL/h/kg, and the median volume of distribution was 186 L/kg.

5.2 Metabolism

Fludarabine phosphate is converted to its active metabolite, 2-fluoro-ara-A, by the enzyme xanthine dehydrogenase. 2-Fluoro-ara-A is the active metabolite of fludarabine phosphate and is responsible for the antitumor activity of the drug.

5.3 Excretion

Fludarabine phosphate is excreted in human milk. The concentration of fludarabine phosphate in human milk was 1.0 mg/mL, and the concentration of 2-fluoro-ara-A in human milk was 0.5 mg/mL. The concentration of fludarabine phosphate in human milk was not known to be above the levels associated with toxicity in the mother.

6. Clinical Studies

6.1 Treatment of Chronic Lymphocytic Leukemia

Fludarabine phosphate has been studied in several clinical trials for the treatment of CLL. In a study of 45 patients with refractory CLL, the overall response rate was 36%, with 9% complete responses and 27% partial responses. The median duration of response was 16 months. The median progression-free survival was 12 months, and the median overall survival was 26 months. The most common adverse events were anemia, neutropenia, and infection.

6.2 Treatment of Non-Hodgkin's Lymphoma

Fludarabine phosphate has been studied in several clinical trials for the treatment of NHL. In a study of 17 patients with relapsed or refractory NHL, the overall response rate was 53%, with 5% complete responses and 48% partial responses. The median duration of response was 16 months. The most common adverse events were anemia, neutropenia, and infection.

6.3 Treatment of Hairy Cell Leukemia

Fludarabine phosphate has been studied in several clinical trials for the treatment of HCL. In a study of 62 patients with relapsed or refractory HCL, the overall response rate was 79%, with 3% complete responses and 76% partial responses. The median duration of response was 24 months. The most common adverse events were anemia, neutropenia, and infection.

7. Adverse Reactions

The most common adverse events associated with fludarabine phosphate treatment are hematological abnormalities, including anemia, neutropenia, and infection. Other adverse events include fatigue, nausea, vomiting, diarrhea, and stomatitis.

8. Dosage and Administration

Fludarabine phosphate is available as a solution for injection in vials containing 10 or 15 mg of fludarabine phosphate. The recommended dose for the treatment of CLL is 20 mg/m2/day for 5 days, followed by a 5-day rest period. The recommended dose for the treatment of NHL is 20 mg/m2/day for 5 days, followed by a 5-day rest period.

9. Overdosage

In the event of an overdose, supportive and symptomatic treatment should be provided. There is no specific antidote for fludarabine phosphate overdosage.

10. Reproduction

10.1 Pregnancy

Fludarabine phosphate is a Pregnancy Category D drug. It is not known whether fludarabine phosphate can cause fetal harm when administered to pregnant women. There are no adequate and well-controlled studies in pregnant women. If fludarabine phosphate is given to a pregnant woman, it should be administered only if the potential benefit justifies the potential risk to the fetus. Fludarabine phosphate is not recommended for use during pregnancy.

10.2 Nursing Mothers

It is not known whether fludarabine phosphate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when fludarabine phosphate is administered to a nursing woman.

11. Contraindications

Fludarabine phosphate is contraindicated in patients with known hypersensitivity to fludarabine phosphate or any of the excipients in the formulation.

12. Warnings and Precautions

12.1 Renal Impairment

Limited pharmacokinetic data for fludarabine phosphate are available in patients with renal impairment. In patients with moderately impaired renal function, the area under the plasma concentration-time curve (AUC) was similar (AUC; 21 vs. 20 ng•h/mL) when administered at a loading dose of 10.5 mg/m2/day followed by a 5-day continuous infusion, and may be multi-faceted.

12.2 Cardiac Dysfunction

Fludarabine phosphate has been associated with cardiac dysfunction, including arrhythmia and cardiovascular events. Fludarabine phosphate should be used with caution in patients with underlying cardiac disease.

12.3 Neurological Dysfunction

Fludarabine phosphate has been associated with neurological dysfunction, including peripheral neuropathy and cerebrovascular accident. Fludarabine phosphate should be used with caution in patients with underlying neurological disease.

13. Interactions

Fludarabine phosphate is a substrate for cytochrome P450 1A2 and may be subject to drug interactions with other drugs that are substrates for this enzyme. Fludarabine phosphate should be used with caution in patients taking drugs that are known to be substrates for cytochrome P450 1A2.

14. Adverse Reactions

The most common adverse events associated with fludarabine phosphate treatment are hematological abnormalities, including anemia, neutropenia, and infection. Other adverse events include fatigue, nausea, vomiting, diarrhea, and stomatitis.

15. Overdosage

In the event of an overdose, supportive and symptomatic treatment should be provided. There is no specific antidote for fludarabine phosphate overdosage.

16. How Supplied/Storage and Handling

Fludarabine phosphate is supplied as a sterile, aqueous solution for injection in vials containing 10 or 15 mg of fludarabine phosphate. The solution should be clear and colorless or slightly yellow. The solution is stable for 1 year when stored in the original container at 2° to 8°C. The solution may be stored at room temperature (up to 25°C) for up to 35 days. The solution should be protected from light exposure for 35 days. The solution should be used within 2 hours of reconstitution. The solution should be used immediately after reconstitution.

17. Laboratory Tests

17.1 Monitoring

Monitoring of blood counts, including white blood cell count, platelet count, and hemoglobin level, should be performed during fludarabine phosphate treatment. Monitoring of renal and hepatic function should also be performed.

18. References