FLUDARABINE PHOSPHATE- fludarabine phosphate injection, solution
Teva Pharmaceuticals, Inc.

Disclaimer: This drug has not been found by FDA to be safe and effective, and this labeling has not been approved by FDA. For further information about unapproved drugs, click here.

Fludarabine Phosphate Injection Unapproved Drug_Shortage

HEALTH CARE PROVIDER LETTER

July 18, 2023

Teva Administrative Offices:
Teva Pharmaceuticals USA, Inc.
Morris Corporate Center
400 Interpace Parkway
Parsippany, NJ 07054
Phone: 1-888-838-2872

Subject: Temporary Importation of Fludarabine Phosphate Injection, USP 50 mg per 2 mL (25 mg/mL),
Mitigation to Address Supply Shortage

Dear Health Care Provider:

To alleviate a critical shortage of Fludarabine Phosphate Injection, USP 50 mg per 2 mL (25 mg/mL) single dose vials in the United States (U.S.) market, Teva has coordinated with the U.S. Food and Drug Administration (FDA) to make available a temporary supply of Fludarabin (Fludarabine Phosphate Injection) Actavis, single dose vials, that is not currently approved under Teva's ANDA (203738). The lots for this temporary supply of Fludarabin Actavis 50 mg per 2 mL (25 mg/mL) marketed in Sweden are manufactured at the same Teva facility that supplied product for the U.S. market. These lots have undergone an internal review by Teva and met all quality specifications.

Effective immediately, Teva will distribute the following presentation of Fludarabin Actavis in the U.S. to address the critical shortage:

Product Name and Description	**Size**	**Marketing Authorization Number**	**NDC***	**Lot Number(s)**
Fludarabin (Fludarabine Phosphate Injection) Actavis, single dose vials	50 mg/2 mL (25 mg/mL)	48182	0480-9772-01	2NM5013 2NM5022

*NDC has been assigned for purposes of supply chain systems product identification and processing only. NDC does NOT appear on the product packaging itself, nor is it encoded in any barcoding.

Indication for Fludarabin Actavis

_Fludarabine Phosphate Injection, USP is indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. The safety and effectiveness of Fludarabine Phosphate Injection, USP in previously untreated or non-refractory patients with CLL have not been established.

Please refer to the FDA-approved Fludarabine Phosphate Injection prescribing information available on DailyMed at DailyMed - FLUDARABINE PHOSPHATE injection, solution (nih.gov) and follow the instructions presented in the FDA-approved package insert, except as noted below about diluting the product in saline (0.9% Sodium Chloride). After June 30, 2023, the U.S. Fludarabine Phosphate Injection prescribing information will be available in the DailyMed Labeling Archives at **https://dailymed.nlm.nih.gov/dailymed/archives/index.cfm?query=a7743c62-2230-4289-92dc-6fc9c61f41d2&date=.**

Important Information Regarding Fludarabin Actavis

There is one important difference in preparation between the FDA-approved product and the supplied product:

- When preparing the Fludarabin Actavis for intravenous administration, the product should only be diluted in saline (0.9% Sodium Chloride) as the stability of diluted EU product has only been tested in saline (0.9% Sodium Chloride).

However, there are no clinically relevant differences in the indication or safety information between the approved U.S package insert and that of the supplied product, or in how healthcare professionals will prescribe or dispense Fludarabin Actavis. Please see the product label comparison table at the end of this letter.

Fludarabin Actavis will be available only by prescription in the U.S. However, the imported lots do not have the statement "Rx only" on their labeling.

There is no barcode on this product for use with U.S. barcode scanning systems. Alternative procedures should be followed to ensure that the correct drug product is being used and administered to individual patients.

In addition, the packaging of the Fludarabin Actavis does not include serialization information and does not meet the product identifier requirements of section 582(b)(2) of the Federal Food, Drug and Cosmetic Act.

Reporting Adverse Events

Healthcare providers should report adverse events associated with the use of Fludarabin Actavis Injection to Teva at 1-888-838-2872, Option 3 and then Option 4.

Adverse events, medication errors or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting Program either online, by regular mail, or by fax:

- Complete and submit the report Online: www.fda.gov/medwatch/report.htm
- Regular mail or Fax: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form or submit by fax to 1-800-FDA-0178 (1-800-332-0178).

If you have any questions about the information contained in this letter, any quality related problems, or questions on the use of Fludarabin Actavis 25 mg/mL single dose vials, please contact Teva Pharmaceuticals USA, Inc. at 1-888-838-2872.

To place an order, please contact Teva directly at 1-888-838-2872, select option 3, then select option 9.

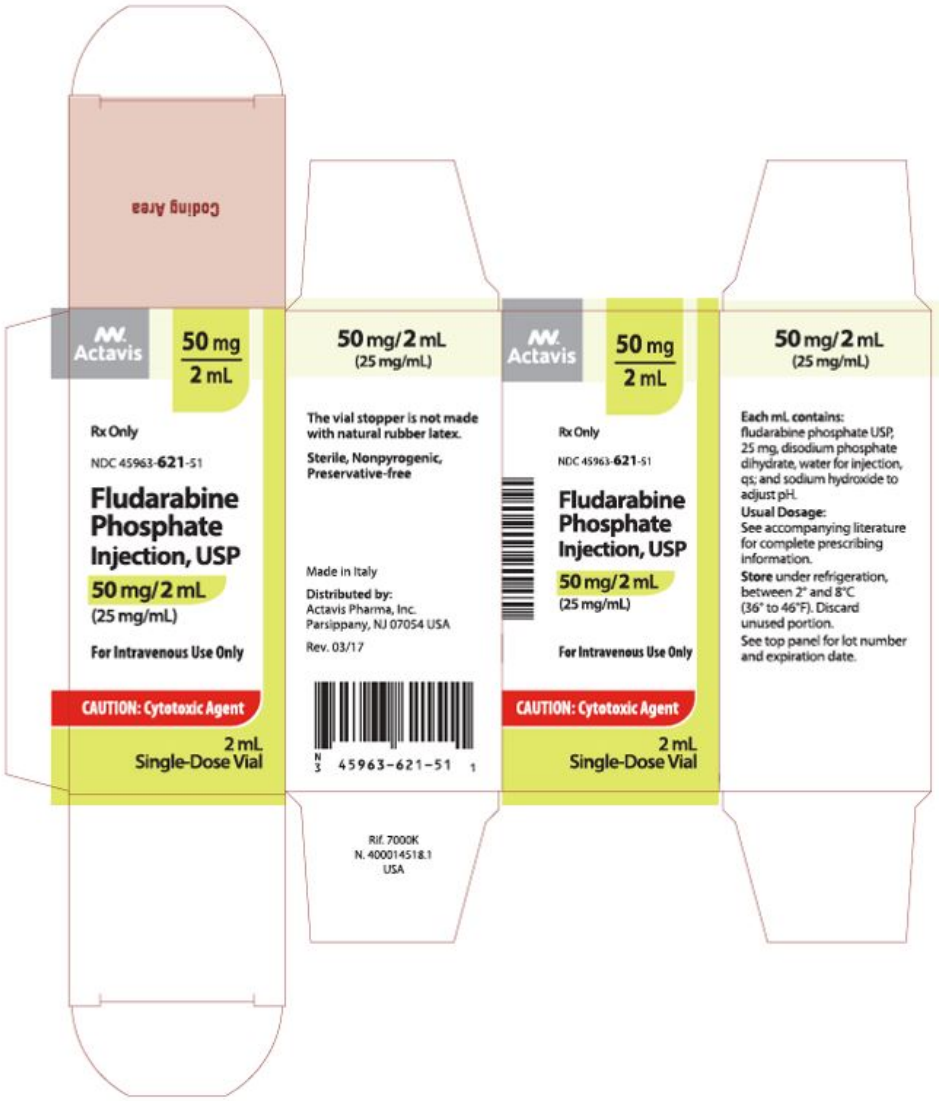
We remain at your disposal to answer any questions you may have about our product and to provide more information if needed.

Sincerely,

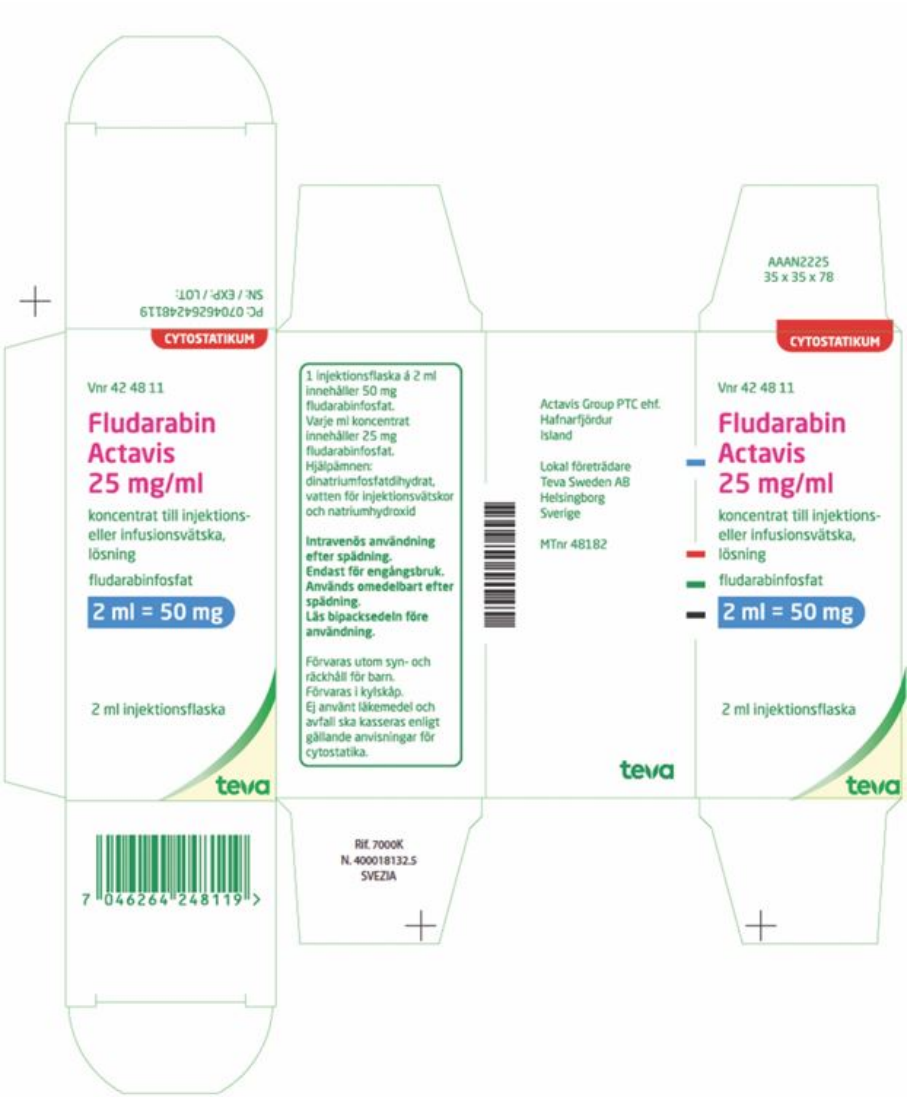
Denisa Hurtukova, MD
Vice President, Head of North America Medical Affairs
Teva Pharmaceuticals

Product Label and Product Characteristics Side-by-Side Comparison Table

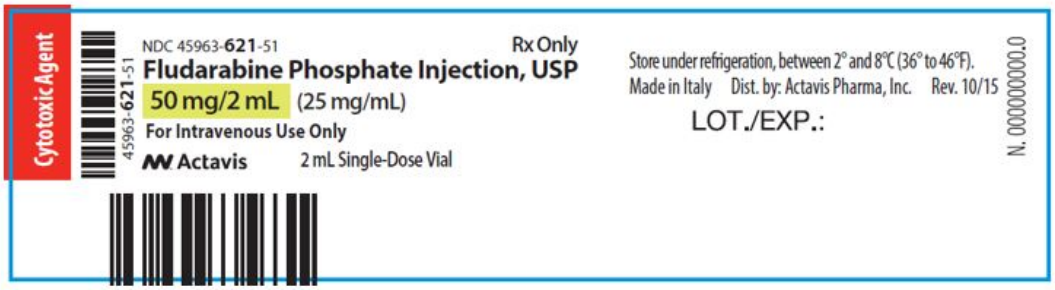
Carton (US FDA Approved)



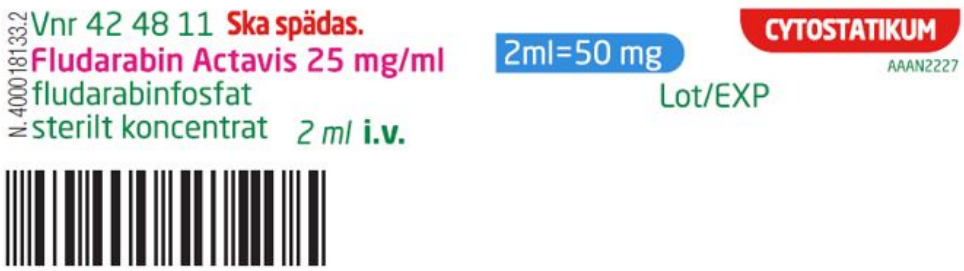
Carton (Import Product)



Vial Label US FDA Approved)



Vial Label (Import Product)



PRESCRIBING INFORMATION

<table>
<tr><th></th><th>US FDA Approved Product</th><th>Import Product</th></tr>
<tr><td>INDICATION</td><td>Fludarabine Phosphate Injection, USP is a nucleotide metabolic inhibitor indicated for:

The treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. Benefit in treatment-naïve or non-refractory CLL patients is not established.</td><td>4.1 Therapeutic indications
Treatment of B-cell chronic lymphocytic leukaemia (CLL) in adult patients with sufficient bone marrow reserves.

First line treatment with fludarabine should only be initiated in adult patients with advanced disease, Rai stages III/IV (Binet stage C) or Rai stages I/II (Binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease.</td></tr>
<tr><td>DOSAGE AND ADMINISTRATION</td><td>2.1 Recommended Dose
The recommended adult dose of Fludarabine Phosphate Injection is 25 mg/m^2 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. These include advanced age, renal impairment, 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 be administered following the achievement of a maximal response and then the drug should be discontinued.

2.2 Renal Impairment

Adjustments to the starting dose are recommended to provide appropriate drug exposure in patients with creatinine clearance 30 to 79 mL/min, as estimated by the Cockroft-Gault equations. These adjustments are based on a pharmacokinetic study in patients with renal impairment. Fludarabine Phosphate Injection should not be administered to patients with creatinine clearance less than 30 mL/min.

Starting Dose Adjustment for Renal Impairment

Creatinine Clearance — Starting: Dose
≥ 80 mL/min — 25 mg/m^2 (full dose)
50 to 79 mL/min — 20 mg/m^2
30 to 49 mL/min — 15 mg/m2
< 30 mL/min — Do not administer

Renally impaired patients should be monitored closely for excessive toxicity and the dose modified accordingly

2.3 Use of Infusion Solutions

Fludarabine Phosphate Injection contains no antimicrobial preservative and should be used within 8 hours of opening. Care must be taken to assure sterility of infusion solutions. Parenteral drug products should be inspected visually for</td><td>4.2 Posology and method of administration Posology
The recommended dose is 25 mg fludarabine phosphate/m² body surface area given daily for

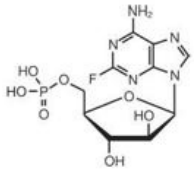
5 consecutive days every 28 days by intravenous route. The required dose (calculated on the basis of the patient’s body surface area) is drawn up into a syringe. For intravenous bolus injection this dose is further diluted in 10 ml of 0.9 % sodium chloride. Alternatively, for infusion, the required dose may be diluted in 100 ml 0.9 % sodium chloride and infused over approximately 30 minutes (see also section 6.6).

The duration of treatment depends on the treatment success and the tolerability of the drug. In CLL patients fludarabine should be administered up to the achievement of best response (complete or partial remission, usually 6 cycles) and then the drug should be discontinued.

Special populations

Renal impairment
Doses should be adjusted for patients with reduced kidney function. If creatinine clearance is between 30 and 70 ml/min, the dose should be reduced by up to 50% and close haematological monitoring should be used</td></tr>
</table>

	particulate matter and discoloration prior to administration, whenever solution and container permit. Fludarabine Phosphate Injection should not be mixed with other drugs.	to assess toxicity (see section 4.4). Fludarabine treatment is contraindicated, if creatinine clearance is < 30 ml/min (see section 4.3). ***Hepatic impairment*** No data are available concerning the use of fludarabine in patients with hepatic impairment. In this group of patients, fludarabine should be used with caution. See also section 4.4. ***Paediatric population*** The safety and efficacy of fludarabine in children below the age of 18 years have not been established. Therefore, fludarabine is not recommended for use in children. ***Elderly*** Since there are limited data for the use of fludarabine in elderly persons (>75 years), caution should be exercised with the administration of fludarabine in these patients (see also section 4.4). In patients over the age of 65 years, creatinine clearance should be measured before start of treatment (see 'Renal impairment' and section 4.4). **Method of administration** /.../ should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. It is strongly recommended that fludarabine should be only administered intravenously. No cases have been reported in which paravenously administered fludarabine led to severe local adverse reactions. However, unintentional paravenous administration must be

		avoided. For instructions on dilution of the medicinal product before administration, see section 6.6.
DESCRIPTION	**11 DESCRIPTION** Fludarabine Phosphate Injection, USP contains fludarabine phosphate, USP, a nucleotide metabolic inhibitor. Fludarabine phosphate, USP is a fluorinated nucleotide analog of the antiviral agent vidarabine, 9-ß-D-arabinofuranosyladenine (ara-A), that is relatively resistant to deamination by adenosine deaminase. The chemical name for fludarabine phosphate, USP is 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono-ß-D-arabinofuranosyl)(2-fluoro-ara-AMP). The molecular formula of fludarabine phosphate is $C_{10}H_{13}FN_5O_7P$ (MW 365.2) and the structure is provided in Figure 1. **Figure 1: Chemical Structure of Fludarabine Phosphate**  Each mL contains 25 mg of the active ingredient fludarabine phosphate, USP, 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, USP is a sterile solution intended for intravenous administration.	**2. QUALITATIVE AND QUANTITATIVE COMPOSITION** Each ml of concentrate for solution for injection or infusion contains 25 mg fludarabine phosphate. Each vial of 2 ml contains 50 mg fludarabine phosphate. For the full list of excipients, see section 6.1. **3. PHARMACEUTICAL FORM** Concentrate for solution for injection or infusion. Clear, colourless or almost colourless solution, pH 7.3-7.7. **6. PHARMACEUTICAL PARTICULARS** **6.1 List of excipients** Disodium phosphate dihydrate Water for injections Sodium hydroxide (for pH adjustment). **6.2 Incompatibilities** This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
HOW SUPPLIED/STORAGE AND HANDLING	**16.1 How Supplied** Fludarabine Phosphate Injection, USP is supplied as a clear, colorless or almost colorless sterile solution containing 25 mg/mL of fludarabine phosphate, USP in a single use vial. NDC 45963-621-51 one carton containing a 50 mg/2 mL glass vial of Fludarabine Phosphate Injection, USP. **16.2 Storage** Store under refrigeration, between 2° and 8°C (36° to 46°F). **16.3 Handling and Disposal** 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. 1-4 Caution should be exercised in the handling and preparation of Fludarabine Phosphate Injection solution. 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	**6.3 Shelf life** Vial before opening: 3 years After dilution: The diluted solution of /.../ in 0.9% sodium chloride is stable for up to 28 days in PVC and PE bags at 2-8°C and at 25°C when protected from light. From a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated

	mucous membranes. Sterile, Nonpyrogenic, Preservative-free. The vial stopper is not made with natural rubber latex.	aseptic conditions. **6.4 Special precautions for storage** Store between 2-8°C. For storage conditions after dilution of the medicinal product, see section 6.3. **6.5 Nature and contents of container** Colourless glass vial (type I) with bromobutylic rubber stopper and metallic cap (aluminium) with polypropylene disk. Vial will be packed with or without a protective plastic overwrap. <u>Pack sizes</u> 2 ml vial 5 x 2 ml vial Not all pack sizes may be marketed. **6.6 Special precautions for disposal and other handling** <u>Dilution</u> The required dose (calculated on the basis of the patient's body surface area) is drawn up into a syringe. For intravenous bolus injection this dose is further diluted in 10 ml of 0.9 % sodium chloride. Alternatively, for infusion, the required dose may be diluted in 100 ml of 0.9 % sodium chloride and infused over approximately 30 minutes (see section 4.2). <u>Inspection prior to use</u> Only clear, colourless to yellowish solutions without particles should be used. /.../ should not be used in case of a defective container. <u>Handling and disposal</u> /.../ should not be handled by pregnant staff. Procedures for proper handling should be followed according to local requirements for cytotoxic drugs. Caution should be exercised in the handling and preparation of the /.../ solution. The use of protective gloves and safety glasses is recommended to avoid exposure in case of

		breakage of the vial or other accidental spillage. If the solution comes into contact with the skin or mucous membranes, the area should be washed thoroughly with soap and water. In the event of contact with the eyes, rinse them thoroughly with copious amounts of water. Exposure by inhalation should be avoided. The medicinal product is for single use only. Any unused medicinal product, spillage or waste material should be disposed of in accordance with local requirements for cytotoxic agents.
CONTRAINDICATIONS	**None**	**4.3 Contraindications** • Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. • Renal impairment with creatinine clearance < 30 ml/min. • Decompensated haemolytic anaemia. • Lactation.
WARNINGS AND PRECAUTIONS *[See (BOXED WARNINGS)]*	**Boxed Warning** **WARNING: SEVERE BONE MARROW SUPPRESSION, CNS TOXICITY, HEMOLYTIC ANEMIA, AND PULMONARY TOXICITY** **Fludarabine Phosphate Injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Fludarabine phosphate injection can severely suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, fludarabine phosphate injection was associated with severe neurologic effects, including blindness, coma, and death. This severe central nervous system toxicity occurred in 36% of patients treated with doses approximately four times greater (96 mg/m^2/day for 5 to 7 days) than the recommended dose. Similar severe central nervous system toxicity, including coma, seizures, agitation and confusion, has been reported in patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia *[see Warnings and Precautions (5.2)].*** **Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia have been reported to occur after one or more cycles of treatment with fludarabine phosphate injection. Patients undergoing treatment with Fludarabine Phosphate Injection should be evaluated and closely monitored for hemolysis *[see***	**No Boxed Warning** **4.4 Special warnings and precautions for use** Myelosuppression Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a Phase I intravenous study in adult solid tumour patients, the median time to nadir counts was 13 days (range, 3 25 days) for granulocytes and 16 days (range, 2 32 days) for platelets. Most patients had haematologic impairment at baseline either as a result of disease or as a result of prior myelosuppressive therapy. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often

Warnings and Precautions (5.3)].

In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of Fludarabine Phosphate Injection in combination with pentostatin is not recommended *[see Warnings and Precautions (5.5)].*

5.1 Dose Dependent Neurologic Toxicities
There are clear dose dependent toxic effects seen with fludarabine phosphate. Dose levels approximately 4 times greater (96 mg/m^2/day for 5 to 7 days) than that recommended for CLL (25 mg/m^2/day for 5 days) were associated with a syndrome characterized by delayed blindness, coma and death. Symptoms appeared from 21 to 60 days following the last dose. Thirteen of 36 patients (36%) who received fludarabine phosphate at high doses

(96 mg/m^2/day for 5 to 7 days) developed this severe neurotoxicity. Similar severe central nervous system toxicity, including coma, seizures, agitation and confusion, has been reported in patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia.

In postmarketing experience neurotoxicity has been reported to occur either earlier or later than in clinical trials (range 7 to 225 days).

The effect of chronic administration of fludarabine phosphate on the central nervous system is unknown; however, patients have received the recommended dose for up to 15 courses of therapy.

Fludarabine phosphate may reduce the ability to drive or use mechanical equipment, since fatigue, weakness, visual disturbances, confusion, agitation and seizures have been observed.

5.2 Bone Marrow Suppression
Severe bone marrow suppression, notably anemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a Phase I study in adult solid tumor patients, the median time to nadir counts was 13 days (range, 3 to 25 days) for granulocytes and 16 days (range, 2 to 32 days) for platelets. Most patients had hematologic impairment at baseline either as a result of disease or as a result of prior myelosuppressive therapy. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of Fludarabine Phosphate Injection requires careful hematologic monitoring.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

5.3 Autoimmune Reactions
Instances of life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemia, autoimmune thrombocytopenia/thrombocytopenic purura (ITP), Evans syndrome, and acquired hemophilia have been

reversible, administration of fludarabine phosphate requires careful haematologic monitoring.

Fludarabine phosphate is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of haematologic and nonhaematologic toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anaemia, neutropenia and thrombocytopenia.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

As with other cytotoxics, caution should be exercised with fludarabine phosphate, when further haematopoietic stem cell sampling is considered.

<u>Autoimmune disorders</u>
Irrespective of any previous history of autoimmune processes or Coombs test status, life-threatening and sometimes fatal autoimmune phenomena (see section 4.8) have been reported to occur during or after treatment with fludarabine phosphate. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with fludarabine phosphate. Patients treated with fludarabine phosphate should be closely monitored for signs of haemolysis.

Discontinuation of therapy

reported to occur after one or more cycles of treatment with fludarabine phosphate in patients with or without a previous history of autoimmune hemolytic anemia or a positive Coombs' test and who may or may not be in remission from their disease. Steroids may or may not be effective in controlling these hemolytic episodes. 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. Patients undergoing treatment with Fludarabine Phosphate Injection should be evaluated and closely monitored for hemolysis. Discontinuation of therapy with Fludarabine Phosphate Injection is recommended in case of hemolysis.

5.4 Transfusion Associated Graft-Versus-Host Disease
Transfusion-associated graft-versus-host disease has been observed after transfusion of non-irradiated blood in fludarabine phosphate treated patients. 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 Pulmonary Toxicity
In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL) in adults, there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of Fludarabine Phosphate Injection in combination with pentostatin is not recommended.

5.6 Pregnancy
Pregnancy Category D
Based on its mechanism of action, fludarabine phosphate can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of fludarabine phosphate injection in pregnant women, Fludarabine phosphate was embryolethal and teratogenic in rats and rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant *[see Use in Specific Populations (8.1)].*

5.7 Male Fertility and Reproductive Outcomes
Males with female sexual partners of childbearing potential should use contraception during and after cessation of fludarabine phosphate therapy. Fludarabine phosphate may damage testicular tissue and spermatozoa. Possible sperm DNA damage raises concerns about loss of fertility and genetic abnormalities in fetuses. The duration of this effect is uncertain *[see Nonclinical Toxicology (13.1)].*

5.8 Tumor Lysis
Tumor lysis syndrome has been associated with fludarabine phosphate treatment. This syndrome has been reported in CLL patients with large tumor burdens. Since fludarabine phosphate can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this complication.

5.9 Renal Impairment
Fludarabine Phosphate Injection must be administered

with fludarabine phosphate is recommended in case of haemolysis. Blood transfusion (irradiated, see below) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.
Neurotoxicity
The effect of chronic administration of fludarabine on the central nervous system is unknown. However, patients tolerated the recommended dose in some studies for relatively long treatment times (for up to 26 courses of therapy).

Patients should be closely observed for signs of neurologic effects.

When used at high doses in dose-ranging studies in patients with acute leukaemia, intravenous fludarabine phosphate was associated with severe neurological effects, including blindness, coma and death. Symptoms appeared from 21 to 60 days from last dose. This severe central nervous system toxicity occurred in 36 % of patients treated intravenously with doses approximately four times greater (96 mg/m²/day for 5-7 days) than the recommended dose. In patients treated at doses in the range of the dose recommended for chronic lymphocytic leukaemia, severe central nervous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion) (see section 4.8).

In post marketing experience neurotoxicity has been reported to occur earlier or later than in clinical trials.

Administration of fludarabine can be associated with leukoencephalopathy (LE), acute toxic leukoencephalopathy (ATL) or reversible posterior leukoencephalopathy

	cautiously in patients with renal impairment. The total body clearance of 2-fluoro-ara-A has been shown to be directly correlated with creatinine clearance. Patients with creatinine clearance 30 to 79 mL/min should have their fludarabine phosphate dose reduced and be monitored closely for excessive toxicity. Fludarabine phosphate should not be administered to patients with creatinine clearance less than 30 mL/min *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)].* In patients aged 65 years or older, creatinine clearance should be measured before start of treatment. **5.10 Vaccination** During and after treatment with Fludarabine Phosphate Injection, vaccination with live vaccines should be avoided.	syndrome (RPLS). These may occur: • at the recommended dose ◦ when fludarabine is given following, or in combination with, medications known to be associated with LE, ATL or RPLS, ◦ or when fludarabine is given in patients with other risk factors such as cranial or total body irradiation, Hematopoietic Cell Transplantation, Graft versus Host Disease, renal impairment, or hepatic encephalopathy. • at doses higher than the recommended dose LE, ATL or RPLS symptoms may include headache, nausea and vomiting, seizures, visual disturbances such as vision loss, altered sensorium, and focal neurological deficits. Additional effects may include optic neuritis, and papillitis, confusion, somnolence, agitation, paraparesis/ quadriparesis, muscle spasticity and incontinence. LE/ ATL/ RPLS may be irreversible, life-threatening, or fatal. Whenever LE, ATL or RPLS is suspected, fludarabine treatment should be stopped. Patients should be monitored and should undergo brain imaging, preferably utilizing MRI. If the diagnosis is confirmed, fludarabine therapy should be permanently discontinued. <u>Tumour lysis syndrome</u> Tumour lysis syndrome has been reported in CLL patients with large tumour burdens. Since fludarabine phosphate can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this

		complication, and hospitalisation may be recommended for these patients during the first course of treatment. <u>Transfusion-associated graft-versus-host disease</u> Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) 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 with a high frequency. Therefore, to minimise 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 should receive irradiated blood only. <u>Skin cancer</u> The worsening or flare up of pre-existing skin cancer lesions as well as new onset of skin cancer have been reported in some patients during or after fludarabine phosphate therapy. <u>Impaired state of health</u> In patients with impaired state of health, fludarabine phosphate should be given with caution and after careful risk/benefit consideration. This applies especially for patients with severe impairment of bone marrow function (thrombocytopenia, anaemia, and/or granulocytopenia), immunodeficiency or with a history of opportunistic infection. <u>Renal impairment</u> The total body clearance of the principle plasma metabolite 2-F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination

			of the compound. Patients with reduced renal function demonstrated an increased total body exposure (AUC of 2F-ara-A). There are limited clinical data available in patients with impairment of renal function (creatinine clearance <70 ml/min). Fludarabine must be administered cautiously in patients with renal insufficiency. In patients with moderate impairment of renal function (creatinine clearance between 30 and 70 ml/min), the dose should be reduced by up to 50% and the patient should be monitored closely (see section 4.2). Fludarabine treatment is contraindicated if creatinine clearance is <30 ml/min (see section 4.3). <u>Hepatic impairment</u> In patients with hepatic impairment fludarabine phosphate should be used with caution because it can cause hepatic toxicity. Fludarabine phosphate should only be administered if the perceived benefit outweighs any potential risk. Such patients should be monitored closely for excessive toxicity and dosage should be modified or the treatment discontinued accordingly. See also section 4.2. <u>Elderly</u> Since there are limited data for the use of fludarabine phosphate in elderly persons >75 years), caution should be exercised with the administration of fludarabine phosphate in these patients (see also section 4.2). In patients aged 65 years or older, creatinine clearance should be measured before start of treatment, see 'Renal impairment' and section 4.2. <u>Pregnancy</u>

Fludarabine phosphate should not be used during pregnancy unless clearly necessary (e.g. lifethreatening situation, no alternative safer treatment available without compromising the therapeutic benefit, treatment cannot be avoided). It has the potential to cause foetal harm (see sections 4.6 and 5.3). Prescribers may only consider the use of fludarabine, if the potential benefits justify the potential risks to the foetus.

Women should avoid becoming pregnant while on fludarabine therapy.

Women of childbearing potential must be apprised of the potential hazard to the foetus.

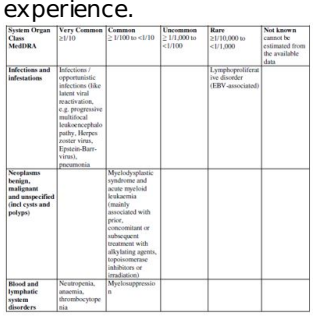
Contraception

Women of child-bearing potential or fertile males must take effective contraceptive measures during and at least for 6 months after cessation of therapy (see section 4.6).

Vaccination
During and after treatment with fludarabine phosphate vaccination with live vaccines should be avoided.

Retreatment options after initial fludarabine treatment
A crossover from initial treatment with fludarabine phosphate to chlorambucil for non-responders to fludarabine phosphate should be avoided because most patients who have been resistant to fludarabine phosphate have shown resistance to chlorambucil.
Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per ml after reconstitution, that is to say essentially 'sodium free'.

4.7 Effects on ability to drive and use machines
Fludarabine phosphate

		may reduce the ability to drive and use machines since e.g. fatigue, weakness, visual disturbances, confusion, agitation and seizures have been observed.
ADVERSE REACTIONS	**6 ADVERSE REACTIONS** 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. Very common adverse reactions include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chills, fatigue, weakness, infection, pneumonia, cough, nausea, vomiting and diarrhea. Other commonly reported events include malaise, mucositis, and anorexia. Serious opportunistic infections have occurred in CLL patients treated with fludarabine phosphate. The most frequently reported adverse reactions and those reactions which are more clearly related to the drug are arranged below according to body system. **6.1 Hematopoietic Systems** Hematologic events (neutropenia, thrombocytopenia, and/or anemia) were reported in the majority of CLL patients treated with fludarabine phosphate. During fludarabine phosphate treatment of 133 patients with CLL, the absolute neutrophil count decreased to less than 500/mm^3 in 59% of patients, hemoglobin decreased from pretreatment values by at least 2 grams percent in 60%, and platelet count decreased from pretreatment values by at least 50% in 55%. Myelosuppression may be severe, cumulative, and may affect multiple cell lines. Bone marrow fibrosis occurred in one CLL patient treated with fludarabine phosphate. Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in post-marketing surveillance. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients. Life-threatening and sometimes fatal autoimmune phenomena such as hemolytic anemias, autoimmune thrombocytopenia/thrombocytopenic purpura (ITP), Evans syndrome, and acquired hemophilia have been reported to occur in patients receiving fludarabine phosphate *[see Warnings and Precautions (5.3)]*. The majority of patients rechallenged with fludarabine phosphate developed a recurrence in the hemolytic process. In post-marketing experience, cases of myelodysplastic syndrome and acute myeloid leukemia, mainly associated with prior, concomitant or subsequent treatment with alkylating agents, topoisomerase inhibitors, or irradiation have been reported. **6.2 Infections** Serious and sometimes fatal infections, including	**4.8 Undesirable effects** Summary of safety profile Based on the experience with the use of fludarabine phosphate, the most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anaemia), infection including pneumonia, cough, fever, fatigue, weakness, nausea, vomiting and diarrhoea. Other commonly reported events include chills, oedema, malaise, peripheral neuropathy, visual disturbance, anorexia, mucositis, stomatitis and skin rash. Serious opportunistic infections have occurred in patients treated with fludarabine phosphate. Fatalities as a consequence of serious adverse events have been reported. Tabulated list of adverse reactions The table below reports adverse events by MedDRA system organ classes (MedDRA SOCs). The frequencies are based on clinical trial data regardless of the causal relationship with fludarabine. The rare adverse reactions were mainly identified from the post-marketing experience.  **System Organ Class MedDRA** / **Very Common** ≥1/10 / **Common** ≥ 1/100 to <1/10 / **Uncommon** ≥ 1/1,000 to <1/100 / **Rare** ≥1/10,000 to <1/1,000 / **Not known** cannot be estimated from the available data **Infections and infestations** — Infections / opportunistic infections (like latent viral reactivation, e.g. progressive multifocal leukoencephalopathy, Herpes zoster virus, Epstein-Barr-virus), pneumonia — Lymphoproliferative disorder (EBV-associated) **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** — Myelodysplastic syndrome and acute myeloid leukaemia (mainly associated with prior, concomitant or subsequent treatment with alkylating agents, topoisomerase inhibitors or irradiation) **Blood and lymphatic system disorders** — Neutropenia, anaemia, thrombocytopenia — Myelosuppression

Serious and sometimes fatal infections, including opportunistic infections and reactivations of latent viral infections such as VZV (herpes zoster), Epstein-Barr virus and JC virus (progressive multifocal leukoencephalopathy) have been reported in patients treated with fludarabine phosphate.

Rare cases of Epstein-Barr (EBV) associated lymphoproliferative disorders have been reported in patients treated with fludarabine phosphate.

In post-marketing experience, cases of progressive multifocal leukoencephalopathy have been reported. Most cases had a fatal outcome. Many of these cases were confounded by prior and/or concurrent chemotherapy. The time to onset ranged from a few weeks to approximately one year after initiating treatment.

Of the 133 adult CLL patients in the two trials, there were 29 fatalities during study, approximately 50% of which were due to infection.

6.3 Metabolic
Tumor lysis syndrome has been reported in CLL patients treated with fludarabine phosphate. This complication may include hyperuricemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and hematuria.

6.4 Nervous System
Objective weakness, agitation, confusion, seizures, visual disturbances, optic neuritis, optic neuropathy, blindness and coma have occurred in CLL patients treated with fludarabine phosphate at the recommended dose. Peripheral neuropathy has been observed in patients treated with fludarabine phosphate and one case of wrist-drop was reported. There have been additional reports of cerebral hemorrhage though the frequency is not known *[see Warnings and Precautions (5)].*

6.5 Pulmonary System
Pneumonia, a frequent manifestation of infection in CLL patients, occurred in 16%, and 22% of those treated with fludarabine phosphate in the MDAH and SWOG studies, respectively. Pulmonary hypersensitivity reactions to fludarabine phosphate characterized by dyspnea, cough and interstitial pulmonary infiltrate have been observed.

In post-marketing experience, cases of severe pulmonary toxicity have been observed with fludarabine phosphate use which resulted in ARDS, respiratory distress, pulmonary hemorrhage, pulmonary fibrosis, pneumonitis and respiratory failure. After an infectious origin has been excluded, some patients experienced symptom improvement with corticosteroids.

6.6 Gastrointestinal System
Gastrointestinal disturbances such as nausea, vomiting, anorexia, diarrhea, stomatitis, and hemorrhage have been reported in patients treated with fludarabine phosphate. Elevations of pancreatic enzyme levels have also been reported.

6.7 Cardiovascular Edema has been frequently reported. One patient developed a pericardial effusion possibly related to treatment with fludarabine phosphate. There have been reports of heart failure and arrhythmia. No other severe cardiovascular events were considered to be drug related.

System Organ Class MedDRA	Very Common ≥1/10	Common ≥ 1/100 to <1/10	Uncommon ≥ 1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Not known cannot be estimated from the available data
Immune system disorders			Autoimmune disorder (including autoimmune haemolytic anaemia, Evan's syndrome, thrombocytopenic purpura, acquired haemophilia, pemphigus)		
Metabolism and nutrition disorders		Anorexia	Tumour lysis syndrome (including renal failure, metabolic acidosis, hyperkalaemia, hypocalcaemia, hyperuricaemia, haematuria, urate crystalluria, hyperphosphataemia)		
Nervous system disorders		Neuropathy peripheral	Confusion	Coma, seizures, agitation	Cerebral haemorrhage, leukoencephalopathy (see section 4.4), acute toxic leukoencephalopathy (see section 4.4), reversible posterior leukoencephalopathy syndrome (RPLS) (see section 4.4)
Eye disorders		Visual disturbance		Blindness, optic neuritis, optic neuropathy	
Cardiac disorders				Heart failure, arrhythmia	
System Organ Class MedDRA	Very Common ≥1/10	Common ≥ 1/100 to <1/10	Uncommon ≥ 1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Not known cannot be estimated from the available data
Respiratory, thoracic and mediastinal disorders	Cough		Pulmonary toxicity (including pulmonary fibrosis, pneumonitis, dyspnoea)		Pulmonary haemorrhage
Gastrointestinal disorders	Vomiting, diarrhoea, nausea	Stomatitis	Gastrointestinal haemorrhage, pancreatic enzymes abnormal		
Hepatobiliary disorders			Hepatic enzyme abnormal		
Skin and subcutaneous tissue disorders		Rash		Skin cancer, necrolysis epidermal toxic (Lyell type), Stevens-Johnson syndrome	
Renal and urinary disorder					Haemorrhagic cystitis
General disorders and administration site conditions	Fever, fatigue, weakness	Oedema, mucositis, chills, malaise			

The most appropriate MedDRA term to describe a certain adverse event is listed. Synonyms or related conditions are not listed, but should be taken into account as well. Adverse event term representation is based on MedDRA version 12.0.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<u>Reporting of suspected adverse reactions</u>
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

6.8 Genitourinary System
Hemorrhagic cystitis has been reported in patients treated with fludarabine phosphate.

6.9 Skin
Skin toxicity, consisting primarily of skin rashes, has been reported in patients treated with fludarabine phosphate. Erythema multiforme, Steven-Johnson syndrome, toxic epidermal necrolysis and pemphigus have been reported, with fatal outcomes in some cases.

6.10 Neoplasms
Worsening or flare-up of pre-existing skin cancer lesions, as well as new onset of skin cancer, has been reported in patients during or after treatment with fludarabine phosphate.

6.11 Hepatobiliary Disorders
Elevations of hepatic enzyme levels have been reported.

6.12 Adverse Reactions from Clinical Trials
Data in Table 1 are derived from the 133 patients with CLL who received fludarabine phosphate in the MDAH and SWOG studies.

Table 1: PERCENT OF CLL PATIENTS REPORTING NON-HEMATOLOGIC ADVERSE REACTIONS

ADVERSE REACTIONS	MDAH (N=101)	SWOG (N=32)
ANY ADVERSE REACTION	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	
SUPRA VENTRICULAR TACHYCARDIA	0	3	
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 3000 adult patients received fludarabine phosphate 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.

7 DRUG INTERACTIONS	**7.1 Pentostatin**	**4.5 Interaction with other medicinal products and other forms of interaction** In a clinical investigation using intravenous fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukaemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate in combination with pentostatin is not recommended. Dipyridamole and other inhibitors of adenosine uptake may reduce the therapeutic efficacy of fludarabine phosphate.

		Clinical studies and in vitro experiments showed that during use of fludarabine in combination with cytarabine the intracellular peak concentration and intracellular exposure of Ara-CTP (active metabolite of cytarabine) increased in leukemic cells. Plasma concentrations of Ara-C and the elimination rate of Ara-CTP were not affected.
8 USE IN SPECIFIC POPULATIONS	**8.1 Pregnancy** *Teratogenic Effects:* Pregnancy Category D. *[see Warnings and Precautions (5.6)]* Based on its mechanism of action, fludarabine phosphate can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of fludarabine phosphate injection in pregnant women, 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 (greater than or equal to 0.5 times the human intravenous dose). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant. **8.3 Nursing Mothers** It is not known whether fludarabine phosphate is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions including tumorigenicity in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother. **8.4 Pediatric Use** Data submitted to the FDA was insufficient to establish efficacy in any childhood malignancy. Fludarabine phosphate was evaluated in 62 pediatric patients (median age 10, range 1 to 21) with refractory acute leukemia (45 patients) or solid tumors (17 patients). Limited pharmacokinetic data for fludarabine phosphate are available in children (ages 1 to 21 years). When fludarabine phosphate was administered as a loading dose over 10 minutes immediately followed by a 5-day continuous infusion, steady-state conditions were reached early. The fludarabine phosphate regimen tested for pediatric	**4.6 Fertility, pregnancy and lactation** Fertility Women of childbearing potential must be apprised of the potential hazard to the foetus. Both sexually active men and women of childbearing potential must take effective contraceptive measures during and at least for 6 months after cessation of therapy (see section 4.4). Pregnancy Preclinical data in rats demonstrated a transfer of fludarabine and/or metabolites through the placenta. The results from intravenous embryotoxicity studies in rats and rabbits indicated an embryolethal and teratogenic potential at the therapeutic doses (see section 5.3). There are very limited data of fludarabine use in pregnant women in the first trimester. Fludarabine should not be used during pregnancy unless clearly necessary (e.g. life-threatening situation, no alternative safer treatment available without compromising the therapeutic benefit, treatment cannot be avoided). Fludarabine has the potential to cause foetal harm. Prescribers may only consider the use of fludarabine, if the potential benefits justify the potential risks to the foetus. Breastfeeding It is not known whether

	lymphocytic leukemia (ALL) patients was a loading bolus of 10.5 mg/m^2/day followed by a continuous infusion of 30.5 mg/m^2/day for 5 days. In 12 pediatric patients with solid tumors, dose-limiting myelosuppression was observed with a loading dose of 8 mg/m^2/day followed by a continuous infusion of 23.5 mg/m^2/day for 5 days. The maximum tolerated dose was a loading dose of 7 mg/m^2/day followed by a continuous infusion of 20 mg/m^2/day for 5 days. Treatment toxicity included bone marrow suppression. Platelet counts appeared to be more sensitive to the effects of fludarabine phosphate than hemoglobin and white blood cell counts. Other adverse events included fever, chills, asthenia, rash, nausea, vomiting, diarrhea, and infection. There were no reported occurrences of peripheral neuropathy or pulmonary hypersensitivity reaction. **8.6 Patients with Renal Impairment** The total body clearance of the principal metabolite 2-fluoro-ara-A correlated with the creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the drug. Renal clearance represents approximately 40% of the total body clearance. Patients with creatinine clearance 30 to 79 mL/min should have their fludarabine phosphate dose reduced and be monitored closely for excessive toxicity. Due to insufficient data, fludarabine phosphate should not be administered to patients with creatinine clearance less than 30 mL/min *[see Dosage and Administration*	this drug or its metabolites are excreted in human milk. However, there is evidence from preclinical data that fludarabine phosphate and/or metabolites transfer from maternal blood to milk. Because of the potential for serious adverse reactions to fludarabine in breast-fed infants, fludarabine is contraindicated in nursing mothers (see section 4.3).
10 OVERDOSAGE	High doses of fludarabine phosphate *[see Warnings and Precautions (5)]* 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 overdosage. Treatment consists of drug discontinuation and supportive therapy.	**4.9 Overdose** High doses of fludarabine phosphate have been associated with leukoencephalopathy, acute toxic leukoencephalopathy, or reversible posterior leukoencephalopathy syndrome (RPLS). Symptoms may include headache, nausea and vomiting, seizures, visual disturbances such as vision loss, altered sensorium, and focal neurological deficits. Additional effects may include optic neuritis, and papillitis, confusion, somnolence, agitation, paraparesis/ quadriparesis, muscle spasticity, incontinence, irreversible central nervous system toxicity characterised 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 overdosage. Treatment consists of drug discontinuation and supportive therapy.
CLINICAL	**12.1 Mechanism of Action**	**5. PHARMACOLOGICAL**

PHARMACOLOGY	Fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The mechanism of action of this antimetabolite is not completely characterized and may be multi-faceted. **12.3 Pharmacokinetics** Phase I studies in humans have demonstrated that fludarabine phosphate is rapidly converted to the active metabolite, 2-fluoro-ara-A, within minutes after intravenous infusion. Consequently, clinical pharmacology studies have focused on 2-fluoro-ara-A pharmacokinetics. After the five daily doses of 25 mg 2-fluoro-ara-AMP/m^2 to cancer patients infused over 30 minutes, 2-fluoro-ara-A concentrations show a moderate accumulation. During a 5-day treatment schedule, 2-fluoroara-A plasma trough levels increased by a factor of about 2. The terminal half-life of 2-fluoro-ara-A was estimated as approximately 20 hours. *In vitro*, plasma protein binding of fludarabine ranged between 19% and 29%. A correlation was noted between the degree of absolute granulocyte count nadir and increased area under the concentration x time curve (AUC).	**PROPERTIES** **5.1 Pharmacodynamic properties** Pharmacotherapeutic group: Antineoplastic agents, purine analogues. ATC-code L01B B05 <u>Mechanism of action</u> /.../ contains fludarabine phosphate, a water-soluble fluorinated nucleotide analogue of the antiviral agent vidarabine, 9-β-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase. Fludarabine phosphate is rapidly dephosphorylated to 2F-ara-A which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2F-ara-ATP. This metabolite has been shown to inhibit ribonucleotide reductase, DNA polymerase α/δ and ε, DNA primase and DNA ligase thereby inhibiting DNA synthesis. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occur. While some aspects of the mechanism of action of 2F-ara-ATP are as yet unclear, it is assumed that effects on DNA, RNA and protein synthesis all contribute to inhibition of cell growth with inhibition of DNA synthesis being the dominant factor. In addition, *in vitro* studies have shown that exposure of CLL lymphocytes to 2F-ara-A triggers extensive DNA fragmentation and cell death characteristic of apoptosis. **5.2 Pharmacokinetic properties** <u>Plasma and urinary pharmacokinetics of fludarabine (2F-ara-A</u>**)** The pharmacokinetics of fludarabine (2F-ara-A) have been studied after intravenous administration by rapid bolus injection and

		short-term infusion as well as following continuous infusion of fludarabine phosphate (fludarabine phosphate, 2F-ara-AMP). No clear correlation was found between 2F ara A pharmacokinetics and treatment efficacy in cancer patients. However, occurrence of neutropenia and haematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses the haematopoiesis in a dose dependent manner. ***Distribution and biotransformation*** 2F-ara-AMP is a water-soluble prodrug of fludarabine (2F-ara-A), which is rapidly and quantitatively dephosphorylated in the human organism to the nucleoside fludarabine (2F ara-A). Another metabolite, 2F-ara-hypoxanthine, which represents the major metabolite in the dog, was observed in humans only to a minor extent. After single dose infusion of 25 mg 2F-ara-AMP per m^2 to CLL patients for 30 minutes 2F-ara-A reached mean maximum concentrations in the plasma of 3.5 - 3.7 µM at the end of the infusion. Corresponding 2F ara A levels after the fifth dose showed a moderate accumulation with mean maximum levels of 4.4 - 4.8 µM at the end of infusion. During a 5 day treatment schedule 2F ara A plasma trough levels increased by a factor of about 2. An accumulation of 2F-ara-A over several treatment cycles can be excluded. Postmaximum levels decayed in three disposition phases with an initial half-life of approximately 5 minutes, an intermediate half-life of 1 - 2 hours and a terminal halflife of approximately 20 hours.

An interstudy comparison of 2F-ara-A pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 ± 40 ml/min/m² (2.2 ± 1.2 ml/min/kg) and a mean volume of distribution (Vss) of 83 ± 55 l/m² (2.4 ± 1.6 l/kg). Data showed a high interindividual variability. Plasma levels of 2F ara-A and areas under the plasma level time curves increased linearly with the dose, whereas half-lives, plasma clearance and volumes of distribution remained constant independent of the dose indicating a dose linear behaviour.

Elimination
2F-ara-A elimination is largely by renal excretion. 40 to 60 % of the administered i.v. dose was excreted in the urine. Mass balance studies in laboratory animals with ^{3}H-2F-ara-AMP showed a complete recovery of radio-labelled substances in the urine.

Characteristics in patients
Individuals with impaired renal function exhibited a reduced total body clearance, indicating the need for a dose reduction. *In vitro* investigations with human plasma proteins revealed no pronounced tendency of 2F-ara-A protein binding.

Cellular pharmacokinetics of fludarabine triphosphate
2F-ara-A is actively transported into leukaemic cells, whereupon it is rephosphorylated to the

monophosphate and subsequently to the di- and triphosphate. The triphosphate 2F-ara-ATP is the major intracellular metabolite and the only metabolite known to have cytotoxic activity. Maximum 2Fara-ATP levels in leukaemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited a

		considerable variation with a median peak concentration of approximately 20 µM. 2F-ara-ATP levels in leukaemic cells were always considerably higher than maximum 2F-ara-A levels in the plasma indicating an accumulation at the target sites. *In vitro* incubation of leukaemic lymphocytes showed a linear relationship between extracellular 2F-ara-A exposure (product of 2F-ara-A concentration and duration of incubation) and intracellular 2F ara ATP enrichment. 2F-ara ATP elimination from target cells showed median half-life values of 15 and 23 hours.
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. The possible adverse effects on fertility in humans have not been adequately evaluated *[see Warnings and Precautions (5.7)].*	**5.3 Preclinical safely data** Systemic toxicity In acute toxicity studies, single doses of fludarabine phosphate produced severe intoxication symptoms or death at dosages about two orders of magnitude above the therapeutic dose. As expected for a cytotoxic compound, the bone marrow, lymphoid organs, gastrointestinal mucosa, kidneys and male gonads were affected. In patients, severe side effects were observed closer to the recommended therapeutic dose (factor 3 to 4) and included severe neurotoxicity partly with lethal outcome (see section 4.9). Systemic toxicity studies following repeated administration of fludarabine phosphate showed also the expected effects on rapidly proliferating tissues above a threshold dose. The severity of morphological manifestations increased with dose levels and duration of dosing and the observed changes were generally considered to be reversible. In principle, the available experience from the therapeutic use of fludarabine phosphate points to a comparable

		toxicological profile in humans, although additional undesirable effects such as neurotoxicity were observed in patients (see section 4.8). Embryotoxicity The results from intravenous animal embryotoxicity studies in rats and rabbits indicated an embryolethal and teratogenic potential of fludarabine phosphate as manifested in skeletal malformations, foetal weight loss and post implantation loss. In view of the small safety margin between the teratogenic doses in animals and the human therapeutic dose as well as in analogy to other antimetabolites which are assumed to interfere with the process of differentiation, the therapeutic use of fludarabine phosphate is associated with a relevant risk of teratogenic effects in humans (see section 4.6). Genotoxic potential, tumorigenicity Fludarabine phosphate has been shown to cause DNA-damage in a sister chromatid exchange test, to induce chromosomal aberrations in an in vitro cytogenetic assay and to increase the rate of micronuclei in the mouse micronucleus test in vivo, but was negative in gene mutation assays and in the dominant lethal test in male mice. Thus, the mutagenic potential was demonstrated in somatic cells but could not be shown in germ cells. The known activity of fludarabine phosphate at the DNA-level and the mutagenicity test results form the basis for the suspicion of a tumorigenic potential. No animal studies which directly address the question of tumorigenicity have been conducted, because the suspicion of an increased risk of second tumours

		due to fludarabine phosphate therapy can exclusively be verified by epidemiological data. Local tolerance According to the results from animal experiments following intravenous administration of fludarabine phosphate, no remarkable local irritation has to be expected at the injection site. Even in case of misplaced injections, no relevant local irritation was observed after paravenous, intraarterial, and intramuscular administration of an aqueous solution containing 7.5 mg fludarabine phosphate/ml. The similarity in nature of the observed lesions in the gastrointestinal tract after intravenous or intragastric dosing in animal experiments supports the assumption that the fludarabine phosphate induced enteritis is a systemic effect.
14 CLINICAL STUDIES	**14.1 Adults** Two single-arm open-label studies of fludarabine phosphate have been conducted in adult patients with CLL refractory to at least one prior standard alkylating-agent containing regimen. In a study conducted by M.D. Anderson Cancer Center (MDAH), 48 patients were treated with a dose of 22 to 40 mg/m^2 daily for 5 days every 28 days. Another study conducted by the Southwest Oncology Group (SWOG) involved 31 patients treated with a dose of 15 to 25 mg/m^2 daily for 5 days every 28 days. 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 and were achieved in heavily pretreated patients. The ability of fludarabine phosphate to induce a significant rate of response in refractory patients suggests minimal cross-resistance with commonly used anti-CLL agents. 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	**Clinical efficacy and safety** A phase III trial in patients with previously untreated B-chronic lymphocytic leukaemia comparing treatment with fludarabine phosphate vs. chlorambucil (40 mg / m² q4 weeks) in 195 and 199 patients respectively showed the following outcome: statistically significant higher overall response rates and complete response rates after 1st line treatment with fludarabine phosphate compared to chlorambucil (61.1% vs. 37.6% and 14.9% vs. 3.4%, respectively); statistically significant longer duration of response (19 vs. 12.2 months) and time to progression (17 vs. 13.2 months) for the patients in the fludarabine phosphate group. The median survival of the two patient groups was 56.1 months for fludarabine phosphate and 55.1 months for chlorambucil, a non-significant difference was also shown with

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. Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Health Care Settings. NIOSH Alert 2004-165.
2. OSHA Technical Manual, TED 1-0.l5A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otim_vi_2.html
3. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm*. 2006; 63: 1172-1193.
4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society

performance status. The proportion of patients reported to have toxicities were comparable between fludarabine phosphate patients (89.7%) and chlorambucil patients (89.9%). While the difference in the overall incidence of haematological toxicities was not significant between the two treatment groups, significantly greater proportions of fludarabine phosphate patients experienced white blood cell (p=0.0054) and lymphocyte (p=0.0240) toxicities than chlorambucil patients. The proportions of patients who experienced nausea, vomiting, and diarrhoea were significantly lower for fludarabine phosphate patients (p<0.0001, p<0.0001, and p=0.0489, respectively) than chlorambucil patients. Toxicities of the liver were also reported for significantly (p=0.0487) less proportions of patients in the fludarabine phosphate group than in the chlorambucil group.

Patients who initially respond to fludarabine phosphate have a chance of responding again to fludarabine phosphate monotherapy.

A randomised trial of fludarabine phosphate vs. cyclophosphamide, adriamycin and prednisone (CAP) in 208 patients with CLL Binet stage B or C revealed the following results in the subgroup of 103 previously treated patients: the overall response rate and the complete response rate were higher with fludarabine phosphate compared to CAP (45% vs. 26% and 13% vs. 6%, respectively); response duration and overall survival were similar with fludarabine phosphate and CAP. Within the stipulated treatment period of 6 months the number of deaths was 9 (fludarabine phosphate) vs. 4 (CAP).

		Post-hoc analyses using only data of up to 6 months after start of treatment revealed a difference between survival curves of fludarabine phosphate and CAP in favour of CAP in the subgroup of pretreated Binet stage C patients.
17 PATIENT COUNSELING INFORMATION	**17.1 Monitoring** Patients should be informed of the importance of periodic assessment of their blood count to detect the development of anemia, neutropenia and thrombocytopenia. **17.2 Laboratory Tests** During treatment, the patient's hematologic profile (particularly neutrophils, red blood cells, and platelets) should be monitored regularly to determine the degree of hematopoietic suppression *[see Warnings and Precautions (5.2)].* **17.3 Pregnancy** Fludarabine phosphate can cause fetal harm when administered to a pregnant woman. Women should be advised to avoid becoming pregnant *[see Warnings and Precautions (5.6)].*	

PRINCIPAL DISPLAY PANEL

Vnr 42 48 11

CYTOSTATIKUM

Fludarabin
Actavis
25 mg/ml

koncetrat till injektions-
eller infusionsvätska,
lösning

fludarabinfosfat

2 ml = 50 mg

2 ml injektionsflaska

English Translation

CYTOSTATICS

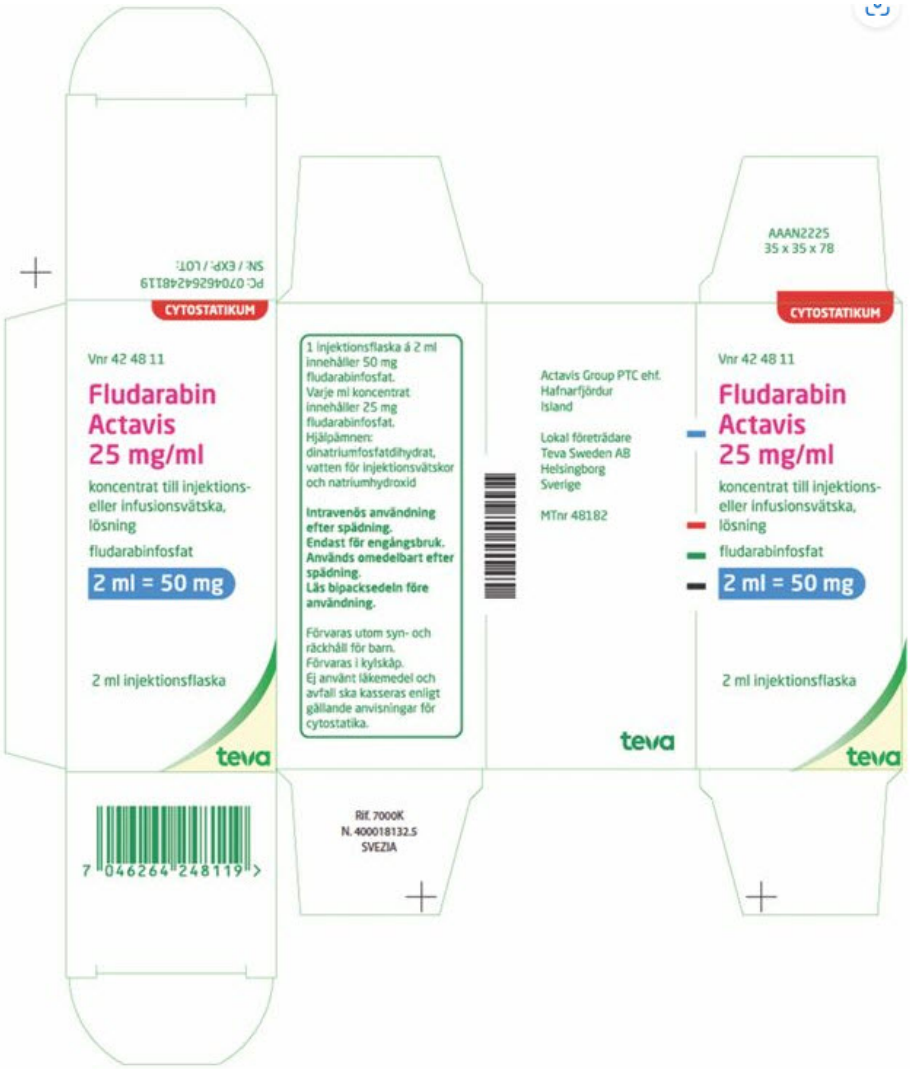
No. 42 48 11

Fludarabin
Actavis
25 mg/ml

concentrate for solution for injection or infusion

fludarabin phosphate
2 ml = 50 mg

2 ml vial



FLUDARABINE PHOSPHATE

fludarabine phosphate injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0480-9772
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
FLUDARABINE PHOSPHATE (UNII: 1X9VK9O1SC) (FLUDARABINE - UNII:P2K93U8740)	FLUDARABINE PHOSPHATE	25 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
SODIUM PHOSPHATE, DIBASIC, DIHYDRATE (UNII: 94255I6E2T)	
WATER (UNII: 059QF0KO0R)	
SODIUM HYDROXIDE (UNII: 55X04QC32I)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0480-9772-01	1 in 1 CARTON	08/31/2023	
1		2 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Unapproved drug for use in drug shortage		08/31/2023	

Labeler - Teva Pharmaceuticals, Inc. (022629579)

Revised: 7/2023

Teva Pharmaceuticals, Inc.