

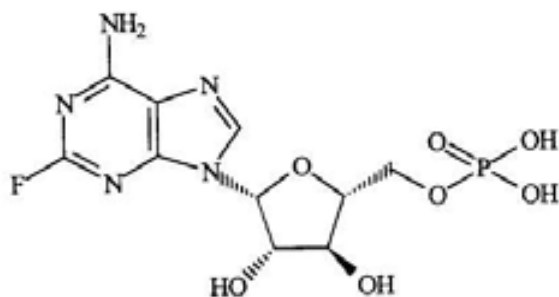
New Zealand Datasheet

FLUDARABINE ACTAVIS

Fludarabine Actavis fludarabine phosphate 50mg powder for injection vial

NAME OF THE MEDICINE

Fludarabine phosphate



Structural Formula

DESCRIPTION

Chemical name: 9-β-D-arabinofuranosyl -2-fluoroadenine 5'-(dihydrogen phosphate).

Molecular formula: C₁₀H₁₃FN₅O₇P.

Molecular Weight: 365.2.

CAS: 75607-67-9

Fludarabine phosphate is a fluorinated nucleotide analogue of the antiviral agent vidarabine (9-beta-d-arabinofuranosyladenine) that is relatively resistant to deamination by adenosine deaminase. When reconstituted as instructed, the pH range of the final solution is 7.2 to 8.2 (target 7.7).

Fludarabine phosphate is a white or almost white, hygroscopic, crystalline powder. It is slightly soluble in water; very slightly soluble in dehydrated alcohol; freely soluble in dimethylformamide.

PHARMACOLOGY

Pharmacology

Fludarabine phosphate is rapidly dephosphorylated to fludarabine (2F-ara-A), which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the

active triphosphate, fludarabine triphosphate (2F-ara-ATP). This metabolite has been shown to inhibit ribonucleotide reductase, DNA polymerase alpha, delta and epsilon, DNA primase and DNA ligase, thereby inhibiting DNA synthesis. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occurs.

While some aspects of the mechanism of action of fludarabine triphosphate 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 chronic lymphocytic leukaemia (CLL) lymphocytes to fludarabine (2F-ara-A) triggers extensive DNA fragmentation and cell death characteristic of apoptosis. Fludarabine phosphate has also been shown to trigger these changes in normal (nonmalignant) lymphoid cells.

Pharmacokinetics

The pharmacokinetics of fludarabine (2F-ara-A) have been studied after intravenous administration by rapid bolus injection, short-term infusion and following continuous infusion as well as after peroral dosing of fludarabine phosphate (2F-ara-AMP).

No clear correlation was found between fludarabine pharmacokinetics and treatment efficacy in cancer patients. However, occurrence of neutropenia and haematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses haemopoiesis in a dose dependent manner.

Distribution and metabolism

Fludarabine phosphate (2F-ara-AMP) is a water soluble prodrug of fludarabine (2F-ara-A), which is rapidly and quantitatively dephosphorylated in humans to the nucleoside fludarabine. After single dose infusion of fludarabine phosphate 25 mg/m² to CLL patients for 30 minutes, fludarabine (2F-ara-A) reached mean maximum concentrations in the plasma of 3.5 to 3.7 microM at the end of the infusion. Corresponding fludarabine (2F-ara-A) levels after the fifth dose showed a moderate accumulation with mean maximum levels of 4.4 to 4.8 microM at the end of infusion. During a five day treatment schedule, fludarabine (2F-ara-A) plasma trough levels increased by a factor of about 2. An accumulation of fludarabine (2F-ara-A) over several treatment cycles can be excluded. Postmaximum levels decayed in three disposition phases with an initial half-life of approximately five minutes, an intermediate half-life of one to two hours and a terminal half-life of approximately 20 hours.

An interstudy comparison of fludarabine (2F-ara-A) pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 mL/minute/m² (2.2 mL/minute/kg) and a mean volume of distribution (V_{ss}) of 83 L/m² (2.4 L/kg). Data showed a high interindividual variability. After intravenous and peroral administration of fludarabine phosphate tablets in doses of 50 to 90 mg, the plasma concentration of fludarabine phosphate and the area under the plasma concentration time curve increased linearly with the dose. Additionally, after intravenous administration half-lives, plasma clearance and volumes of distribution remained constant independent of the dose indicating a dose linear behaviour.

After peroral fludarabine phosphate (2F-ara-AMP) doses, maximum fludarabine (2F-ara-A) plasma levels reached approximately 20 to 30% of corresponding intravenous levels at the end of infusion and occurred one to two hours post dose. The mean systemic fludarabine (2F-ara-A) availability was in the range of 50 to 65% following single and repeated doses and was similar after ingestion of a solution or immediate release tablet formulation. After peroral dosing of fludarabine phosphate (2F-ara-AMP) with concomitant food intake a slight increase (< 10%) of systemic availability (AUC), a slight

decrease of maximum plasma levels (C_{max}) of fludarabine (2F-ara-A) and a delayed time of occurrence of C_{max} was observed. Terminal half-lives were unaffected. In vitro investigations with human plasma proteins revealed no pronounced tendency of fludarabine (2F-ara-A) protein binding.

Excretion

Fludarabine (2F-ara-A) elimination is largely by renal excretion. 40 to 60% of the administered intravenous dose was excreted in the urine. Mass balance studies in laboratory animals with ³H-2F-ara-AMP showed a complete recovery of radiolabelled substances in the urine.

Impaired renal function

Individuals with impaired renal function exhibited a reduced total body clearance, indicating the need for a dose reduction. Three groups of CLL/non-Hodgkin's lymphoma patients with differing creatinine clearance, > 70 (n = 10), 30 to 70 (n = 9), < 30 (n = 2) mL/minute, were compared. After a single dose of fludarabine 25 mg by 30 minute intravenous infusion, AUC increased 16% in the second group and 116% in the third group relative to the first group. Multiple adjusted intravenous doses were then given over five days. The first group received 25 mg/m²/day, the second 20 mg/m²/day and the third 15 mg/m²/day. AUC was equivalent in the first and second groups, but increased 41% in the third group. (Note. Fludarabine is not recommended for patients in the third group (see Contraindications).) There was a statistically significant inverse correlation between fludarabine AUC and creatinine clearance.

Cellular pharmacokinetics of fludarabine triphosphate

Fludarabine (2F-ara-A) is actively transported into leukaemic cells, whereupon it is rephosphorylated to the monophosphate and subsequently to the diphosphate and triphosphate. The triphosphate 2F-ara-ATP is the major intracellular metabolite and the only metabolite known to have cytotoxic activity. Maximum 2F-ara-ATP levels in leukaemic lymphocytes of CLL patients were observed at a median of four hours and exhibited a considerable variation with a median peak concentration of approximately 20 microM. 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.

CLINICAL TRIALS

The following information refers to the use of Fludarabine phosphate in first line chronic lymphocytic leukaemia. Intravenous fludarabine 25 mg/m² on days 1 to 5 of a 28 day cycle significantly delayed disease progression compared with comparators in the first line treatment of B-cell CLL in three randomised controlled trials (see Tables 1 to 3). A difference in survival was not shown due to insufficient follow-up and confounding as a result of crossovers. There was a median 7 and maximum 21 treatment cycles.

TABLE 1

Intravenous Fludarabine – Trial 1 (Spirano) – median duration 8 cycles versus chlorambucil 30mg/m² orally on days 1, 15 plus methylprednisolone 40 mg/m² intramuscularly on days 1 to 5 and 15 to 19 every 28 days (C/MP)

	Fludarabine n = 75	C/MP n = 75	Difference (95% CI)
Complete reponse rate* %	25	21	4 (-10, 18)
Median Time to progression (months)	26	21	Hazard ratio = 0.53 (0.35, 0.79)
Median survival (months)	> 48	> 48	

* US National Cancer Institute Working Group 1988 (NCI) criteria

TABLE 2

Intravenous (IV) Fludarabine – Trial 2 (Inveresk) – duration 6 cycles versus cyclophosphamide 750 mg/m² IV on day 1 plus Doxorubicin 50 mg/m² IV on day 1 plus Prednisone 40 mg/m² orally on days 1 to 5 every 28 days (CAP)

	Fludarabine n = 53	C/MP n = 52	Difference (95% CI)
Complete reponse rate* %	17	8	9 (6, 28)
Median time to progression (months)	41	17	Hazard ratio = 0.46 (0.30, 0.71)
Median survival (months)	65	53	

* International Workshop on CLL criteria 1989 (IWCLL) criteria

TABLE 3

Intravenous Fludarabine – Trial 3 (CALGB) – median duration 7 cycles versus chlorambucil 40mg/m² orally on day 1 every 28 days.

	Fludarabine n = 175	Chlorambucil n = 178	Difference (95% CI)
Complete reponse rate* %	15	3	12 (4,19)
Median Time to Progression (months)	17	13	Hazard ratio = 0.55 (0.39, 0.76)
Median survival (months)	56	55	4

* Modified US National Cancer Institute Working Group 1988 criteria

Fludarabine tablets were assessed in an uncontrolled trial in 81 patients for first line treatment of B-cell CLL. The dose was 40 mg/m² on days 1 to 5 of each 28 day treatment cycle for a mean of six cycles. Fewer patients in this trial had Rai stage III/IV disease (22%) than in the intravenous fludarabine trials (35 to 50%). The median time to disease progression had not been reached at the time of the analysis, but exceeded 38 months, which is comparable or better than the result in the intravenous trials. The NCI complete response rate was 12% and overall response rate 80%. In a subgroup analysis, patients with Rai stage III or IV disease had a response rate of 61% which is comparable to that observed in this subgroup in the IV studies. There were no data on survival.

INDICATIONS

Treatment of B-cell chronic lymphocytic leukaemia.

CONTRAINDICATIONS

Fludarabine phosphate is contraindicated in those patients who are hypersensitive to this drug or its components, in renally impaired patients with creatinine clearance < 30 mL/min and in patients with haemolytic anaemia.

Fludarabine phosphate is contraindicated during pregnancy and lactation.

PRECAUTIONS

Neurotoxicity

When used at high doses in dose ranging studies in patients with acute leukaemia, fludarabine phosphate was associated with severe neurological effects including blindness, coma and death. This severe central nervous system (CNS) toxicity occurred in 36% of patients treated intravenously with doses approximately four times greater (96 mg/m²/day for five to seven days) than the dose recommended for treatment of CLL. In patients treated at doses in the range of the dose recommended for CLL, severe CNS toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion).

In postmarketing experience, neurotoxicity has also been reported to occur, with a latency ranging from 7 to 225 days after the last dose of fludarabine phosphate.

The effect of chronic administration of fludarabine phosphate on the central nervous system is unknown. However patients tolerated the recommended dose in some studies for relatively long treatment times, whereby up to 26 courses of therapy were administered.

Myelosuppression

Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a phase I study in solid tumour patients, the median time to nadir counts was 13 days (range 3 to 25 days) for granulocytes and 16 days (range 2 to 32) for platelets. Most patients had haematological 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 requires careful haematological monitoring.

Fludarabine phosphate is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of haematological and nonhaematological toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anaemia, neutropenia and thrombocytopenia. In such cases, as a general rule, the dose of myelosuppressive agents should be reduced or the dosage interval extended.

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 two months to one year. These episodes have occurred both in previously treated or untreated patients.

Disease progression

Disease progression and transformation (e.g. Richter's syndrome) have been commonly reported in CLL patients.

Transfusion associated graft versus host disease

Transfusion associated graft versus host disease has been observed after transfusion of nonirradiated blood in Fludarabine phosphate treated patients. Fatal outcome as a consequence of this disease has been reported with a high frequency. Therefore patients who require blood transfusion and who are undergoing, or who have received, treatment with Fludarabine phosphate should receive irradiated blood only.

Skin cancer lesions

The 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 Fludarabine phosphate therapy.

Tumour lysis syndrome

Tumour lysis syndrome associated with Fludarabine phosphate treatment 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.

Autoimmune phenomena

Irrespective of any previous history of autoimmune processes or Coombs' test status, life threatening and sometimes fatal autoimmune phenomena (e.g. autoimmune haemolytic anaemia, autoimmune thrombocytopenia, thrombocytopenic purpura, pemphigus, Evans' syndrome) 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 undergoing treatment with Fludarabine phosphate should be closely monitored for signs of autoimmune haemolytic anaemia (decline in haemoglobin linked with haemolysis and positive Coombs' test). Discontinuation of therapy with fludarabine phosphate is recommended in case of haemolysis. Blood transfusion (irradiated) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.

Use in specialised groups

Impaired state of health

Patients who have advanced stage disease, hypoalbuminaemia, reduced platelet count or haemoglobin levels, white cell count above $50 \times 10^9/L$, significant hepatic or spleen enlargement, extensive prior therapy or poor performance status are at risk of serious and sometimes fatal toxicity during the first six months of treatment.

Fludarabine treatment may be associated with a spectrum of infections different from those seen with neutropenia from standard chemotherapy drugs. Prophylactic treatment should be considered in patients at increased risk of developing opportunistic infections, which include, but are not limited to, pneumocytis, fungi and herpes virus infections.

The dose of $25 \text{ mg/m}^2/\text{day}$ for five days by intravenous infusion may be greater than needed in some patients, especially those at risk and consideration should be given to using a lower dose in such patients.

Impaired renal function

There are limited data in dosing of patients with renal insufficiency. Careful monitoring for haematological toxicity is required and possible dose reductions of Fludarabine phosphate in patients with renal impairment and patients with depressed white cell count and platelet counts or patients with infection or bleeding may be required.

The total body clearance of 2-fluoro-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). Limited clinical data are available in patients with impairment of renal function (creatinine clearance below 70 mL/minute). Therefore, if renal impairment is clinically suspected, or in patients over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70 mL/minute, the dose should be reduced in proportion to the reduced creatinine clearance and close haematological monitoring should be used to assess toxicity. Fludarabine phosphate treatment is contraindicated if creatinine clearance is $< 30 \text{ mL/minute}$.

Impaired hepatic function

No data are available concerning the use of Fludarabine phosphate in patients with hepatic impairment. In this group of patients, Fludarabine phosphate should be used with caution, and administered if the potential benefit outweighs any potential risk.

Use in the elderly

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.

Carcinogenesis, mutagenesis, impairment of fertility

Carcinogenesis, mutagenesis

No animal carcinogenicity studies with Fludarabine phosphate have been conducted. However positive findings in carcinogenicity studies with other cytotoxic drugs and the positive genotoxicity findings with fludarabine phosphate suggest that Fludarabine

phosphate has carcinogenic potential. Fludarabine phosphate has been shown not to cause gene mutations in bacterial and mammalian cells in vitro. Chromosomal aberrations were observed in an in vitro assay using Chinese hamster ovary (CHO) cells under metabolically activated conditions. Fludarabine phosphate has also been shown to be clastogenic in the in vivo mouse micronucleus test. In addition, fludarabine phosphate was shown to cause increased sister chromatid exchanges using an in vitro sister chromatid exchange (SCE) assay under both metabolically activated and nonactivated conditions.

Impairment of fertility

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 dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. These results indicate that fludarabine phosphate may adversely affect male fertility, but this has not been directly investigated in studies of reproductive function. No information is available from animal studies on potential effects on female fertility. The possible adverse effects on fertility in humans have not been adequately evaluated.

Vaccination

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

Effect on ability to drive or operate machinery

Fludarabine phosphate may reduce the ability to drive or use machines, since fatigue, weakness, visual disturbances, confusion, agitation and seizures have been observed. Patients experiencing such adverse effects should avoid driving and using machines.

Use in pregnancy (Category D)

Category D - Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

One case of fludarabine phosphate use during early pregnancy leading to skeletal and cardiac malformation in the newborn has been reported.

Fludarabine phosphate has been shown to be embryotoxic and/or teratogenic in animal studies. Preclinical data in rats demonstrated a transfer of fludarabine phosphate and /or metabolites through the feto-placental barrier. In view of the small exposure margin between 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.

Females of childbearing potential or males must take contraceptive measures during and at least for six months after cessation of therapy. If the patient becomes pregnant while taking this drug, the patient should be advised of the potential hazard to the foetus.

Use in lactation

It is not known whether this drug is 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 in breastfed infants from Fludarabine phosphate, breastfeeding should be discontinued for the duration of Fludarabine phosphate therapy.

Use in children

The safety and effectiveness of Fludarabine phosphate in children have not been established.

Interactions with other medicines

In a clinical investigation using 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.

A pharmacokinetic drug interaction was observed in AML patients during combination therapy with fludarabine phosphate and Ara-C (cytarabine). Clinical studies and in vitro experiments with cancer cell lines demonstrated elevated intracellular Ara-CTP levels in combination with Fludarabine phosphate treatment.

The therapeutic efficacy of Fludarabine phosphate may be reduced by dipyridamole and other inhibitors of adenosine uptake.

In clinical investigation, pharmacokinetic parameters after peroral administration were not significantly affected by concomitant food intake.

ADVERSE EFFECTS

Based on the experience with the intravenous use of fludarabine phosphate, the most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anaemia), fever, chills and infection including pneumonia, cough, fever, fatigue, weakness, nausea, vomiting, and diarrhoea. Other commonly reported events include chills, oedema, malaise, anorexia, nausea, peripheral neuropathy, visual disturbances, diarrhoea, stomatitis, skin rashes and mucositis. Serious opportunistic infections have occurred in CLL patients treated with fludarabine phosphate. Fatalities as a consequence of serious adverse events have been reported.

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 phosphate. The rare adverse reactions were mainly identified from post marketing experience.

System Organ Class – MedDRA v9.1	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1000 to <1/100	Rare ≥1/10000 to <1/1000
Infections and infestations	Infections / opportunistic infections (like latent viral reactivation e.g. Herpes zoster virus, Epstein-Barr-virus, progressive multifocal			Lymphoproliferative disorder (EBV-associated)

	leucoencephalopathy), pneumonia			
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)		Skin cancer
Blood and lymphatic system disorders	Neutropenia, anaemia, thrombocytopenia	Myelosuppression		
Immune system disorders			Autoimmune disorder (incl autoimmune haemolytic anaemia, thrombocytopenic purpura, pemphigus, Evan's syndrome, acquired haemophilia)	
Metabolism and nutrition disorders		Anorexia	Tumor lysis syndrome (incl renal failure, hyperkalemia, metabolic acidosis, haematuria, urate crystalluria, hyperuricaemia, hyperphosphataemia, hypocalcaemia)	
Nervous system disorders		Neuropathy peripheral	Confusion	Agitation, seizures, coma
Eye disorders		Visual disturbance		Optic neuritis, optic neuropathy, blindness
Cardiac disorders				Heart failure, arrhythmia
Respiratory, thoracic and mediastinal disorders	Cough		Pulmonary toxicity (incl dyspnoea, pulmonary fibrosis, pneumonitis)	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea	Stomatitis	Gastrointestinal haemorrhage, pancreatic enzymes	

			abnormal	
Hepatobiliary disorders			Hepatic enzyme abnormal	
Skin and subcutaneous tissue disorders		Rash		Stevens-Johnson syndrome, necrolysis epidermal toxic (Lyell type)
Renal and urinary disorder				Haemorrhagic cystitis
General disorders and administration site conditions	Fever, fatigue, weakness	Chills, malaise, oedema, mucositis		

DOSAGE AND ADMINISTRATION

Formulation for intravenous use

Fludarabine Actavis 50 should be administered under the supervision of a qualified doctor experienced in the use of antineoplastic therapy.

It is strongly recommended that Fludarabine Actavis 50 should only be administered intravenously. Paravenous administration must be avoided.

Adults

The recommended dose is 25 mg/m² body surface, given daily for five consecutive days every 28 days by the intravenous route. Each vial is to be made up with water for injections 2 mL. Each mL of the resulting solution will contain Fludarabine phosphate 25 mg.

The required dose (calculated on the basis of the patient's body surface) is drawn up into a syringe. For intravenous bolus injection, this dose is further diluted in physiological saline 10 mL. Alternatively, the required dose drawn up in a syringe may be diluted in physiological saline 100 mL and infused over approximately 30 minutes.

The duration of treatment depends on the treatment success and the tolerability of the drug. Fludarabine Actavis 50 should be administered up to achievement of best response (complete or partial remission, usually six cycles) and then the drug should be discontinued.

Toxicity

Dosage may be decreased or delayed based on evidence of haematological and non-haematological toxicity. Doctors should consider delaying or discontinuing the drug if toxicity occurs.

Impaired state of health

A number of clinical settings may predispose to increased toxicity from Fludarabine Actavis 50. These include advanced age, renal insufficiency and bone marrow impairment (see Precautions, Use in specialised groups, Impaired state of health). Such patients should be monitored closely for excessive toxicity and the dose modified accordingly.

Impaired renal function

Dosage reduction is required in renally impaired patients. See Actions, Pharmacokinetics, Impaired renal function, and Precautions, Use in specialised groups.

Retreatment options after initial Fludarabine phosphate treatment

Patients who primarily respond to Fludarabine Actavis 50 have a good chance of responding again to Fludarabine phosphate monotherapy. A crossover from initial treatment with Fludarabine Actavis 50 to chlorambucil for nonresponders to Fludarabine phosphate should be avoided. In a clinical trial, 46 subjects who failed initial fludarabine therapy were treated with chlorambucil 40 mg/m² every 28 days. Only one subject (2%) achieved a partial response.

Instructions for use/ handling of the intravenous dose form

Fludarabine Actavis 50 should be prepared for parenteral use by aseptically adding sterile water for injections. When reconstituted with sterile water for injections 2 mL, the solid cake should fully dissolve in 15 seconds or less. Each mL of the resulting solution will contain fludarabine phosphate 25 mg, mannitol 25 mg and sodium hydroxide to adjust pH to 7.7. The pH range for the final product is 7.2 to 8.2. In clinical studies the product has been diluted in 100 mL or 125 mL of glucose 5% injection or sodium chloride 0.9%.

Fludarabine Actavis 50 should not be handled by pregnant staff.

Procedures for proper handling and disposal should be observed. Consideration should be given to handling and disposal according to guidelines used for cytotoxic drugs. Any spillage or waste material may be disposed of by incineration.

Caution should be exercised in the handling and preparation of the Fludarabine Actavis 50 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 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.

Incompatibilities

The formulation for intravenous use must not be mixed with other drugs.

OVERDOSAGE

In Australia, the Poisons Information Centre, telephone number 131 126, should be contacted for advice on the management of an overdose.

In New Zealand, the National Poisons Centre, telephone number 0800 POISON, or 0800 764 766, should be contacted for advice on the management of an overdose.

Symptoms

High doses of fludarabine phosphate have been associated with an 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.

Treatment

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

PRESENTATION AND STORAGE CONDITIONS

Powder for injection (sterile, glass vial): 50 mg. This product also contains mannitol and sodium hydroxide.

Store below 25°C. This product is for single use in one patient only. Discard any residue.

Physiochemical stability of Fludarabine Actavis 50 has been demonstrated for a maximum storage period and storage temperature for the reconstituted solution of 7 days, at 2°C-8°C or 8 hours at room temperature (25°C). However, to reduce microbiological hazard, dilute the reconstituted solution as soon as practicable after reconstitution and administer the diluted solution as soon as practicable after dilution. If storage is necessary, hold at 2°-8°C for a total time of not more than 24 hours after reconstitution or at room temperature (25°C) for a total time of not more than 6 hours.

NAME AND ADDRESS OF THE SPONSOR

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