

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fludarabine Phosphate 25mg/ml concentrate for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for injection/infusion contains 25 mg fludarabine phosphate.

Each vial of 2 ml contains 50 mg fludarabine phosphate.

Excipient with known effect:

Contains sodium (from sodium hydroxide) at amounts up to 23 mg per ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection/infusion.

Clear, colourless or almost colourless solution, pH 7.3-7.7.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves. First line treatment with Fludarabine Phosphate should only be initiated in 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.

4.2 Posology and method of administration

Fludarabine Phosphate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

Posology

Adults

The recommended dose is 25 mg fludarabine phosphate /m² body surface given daily for 5 consecutive days every 28 days by the intravenous route. 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 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 optimal duration of treatment has not been clearly established. The duration of treatment depends on the treatment success and the tolerability of the drug. It is recommended that Fludarabine Phosphate be administered up to the achievement of response (usually 6 cycles) and then the drug should be discontinued.

Hepatic impairment

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 perceived benefit outweighs any potential risk (see also section 4.4).

Renal impairment

Doses should be adjusted for patients with reduced renal 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 to assess toxicity. For further information see section 4.4.

Fludarabine Phosphate treatment is contraindicated, if creatinine clearance is <30 ml/min (see section 4.3).

Paediatric population

Fludarabine is not recommended for use in children and adolescents below age 18, due to a lack of data on safety and efficacy.

Elderly population

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).

Method of administration

Fludarabine Phosphate should only be administered intravenously.

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

4.4 Special warnings and precautions for use

Neurotoxicity

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 (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, 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 for treatment. 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.

Impaired state of health

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.

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 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 non-haematological 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 sampling is considered.

Transfusion-associated graft-versus-host disease

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 minimize the risk, patients who require blood transfusion and who are undergoing, or who have received, treatment with Fludarabine Phosphate should receive irradiated blood only.

Skin cancer

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 to occur during or after fludarabine phosphate therapy.

Tumour lysis syndrome

Tumour lysis syndrome has been reported in 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 disorders

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 re-challenge with fludarabine phosphate. Patients treated with Fludarabine Phosphate should be closely monitored for signs of haemolysis.

Discontinuation of therapy with Fludarabine Phosphate is recommended in case of haemolysis. Blood transfusion (irradiated, see above) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.

Hepatic impairment

Fludarabine phosphate should be used with caution in patients with hepatic impairment due to the risk of liver toxicity. Fludarabine phosphate should be administered only if the perceived benefit outweighs any potential risk. These patients should be closely observed for signs of increased toxicity and the dosing should be modified or the treatment discontinued if indicated (see section 4.2).

Renal impairment

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).

Older people

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. In patients aged 65 years or older, creatinine clearance should be measured before start of treatment, see "Renal impairment" and section 4.2.

Paediatric population

No data are available concerning the use of fludarabine phosphate in the paediatric population. Therefore, treatment with Fludarabine Phosphate in children and adolescents below age 18 is not recommended.

Pregnancy

Fludarabine Phosphate 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). 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

Females of child-bearing potential and sexually active 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, i.e. essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interactions

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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Preclinical data in rats demonstrated a transfer of fludarabine and/or metabolites through the placenta. The results from intravenous embryo toxicity studies in rats and rabbits indicated an embryo lethal 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 this drug or its metabolites are excreted in human milk. However, there is evidence from preclinical data that fludarabine 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).

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).

4.7 Effects on ability to drive and use machines

Fludarabine Phosphate may reduce the ability to drive and use machines since fatigue, weakness, agitation, confusion, seizures and visual disturbances have been observed.

4.8 Undesirable effects

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 stomatitis, mucositis, malaise, anorexia, oedema, chills, peripheral neuropathy, visual disturbances and skin rashes. Serious opportunistic infections have occurred in 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. The rare adverse reactions were mainly identified from the post-marketing experience.

The following frequencies are the basis for assessing undesirable effects:

Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Not known (cannot be estimated from the available data).

System Organ Class MedDRA	Frequency	Adverse events
Infections and infestations	Very Common	Infections/ Opportunistic infections (like latent viral reactivation e.g. progressive multifocal leukoencephalopathy, Herpes zoster virus, Epstein-Barr-virus), Pneumonia
	Rare	Lympho-proliferative disorder (EBV-associated)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common	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	Very Common	Neutropenia, anaemia, thrombocytopenia
	Common	Myelo-suppression
Immune system disorders	Uncommon	Autoimmune disorder (including autoimmune haemolytic anaemia, Evans syndrome, thrombocytopenic purpura, acquired haemophilla, pemphigus)
Metabolism and nutrition disorders	Common	Anorexia
	Uncommon	Tumor lysis syndrome (including renal failure, metabolic acidosis, hyperkalaemia hypocalcaemia, hyperuricaemia, haematuria, urate crystalluria, hyper-phosphatemia)
Nervous system disorders	Common	Neuropathy peripheral
	Uncommon	Confusion
	Rare	Coma, seizures, agitation
	Not known	Cerebral haemorrhage
Eye disorders	Common	Visual disturbance
	Rare	Blindness, optic neuritis, optic neuropathy
Cardiac disorders	Rare	Heart failure arrhythmia
Respiratory thoracic and mediastinal disorders	Very common	Cough
	Uncommon	Pulmonary toxicity (including pulmonary fibrosis, pneumonitis, dyspnoea)
	Not known	Pulmonary haemorrhage
Gastrointestinal	Very common	Vomiting, diarrhoea, nausea

disorders	Common	Stomatitis
	Uncommon	Gastro-intestinal haemorrhage, pancreatic enzymes abnormal
Hepatobiliary disorders	Uncommon	Hepatic enzyme abnormal
Skin and subcutaneous tissue disorders	Common	Rash
	Rare	Skin cancer, necrolysis epidermal toxic (Lyell type), Stevens-Johnson syndrome
Renal and urinary disorder	Not known	Haemorrhagic cystitis
General disorders and administration site conditions	Very common	Fever, fatigue, weakness
	Common	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.

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

Reporting of suspected adverse reactions

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, purine analogues. ATC-code L01B B05

Mechanism of action

Fludarabine Phosphate 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.

Clinical efficacy and safety

A phase III trial in patients with previously untreated B-chronic lymphocytic leukaemia comparing treatment with fludarabine phosphate vs. chlorambucil (40mg / 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 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.

5.2 Pharmacokinetic properties

Plasma and urinary pharmacokinetics of fludarabine (2F-ara-A)

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.

Occurrence of neutropenia and haematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses the haematopoiesis in a dose dependent manner.

Absorption, distribution and biotransformation

2F-ara-AMP is a water-soluble prodrug, which is rapidly and quantitatively dephosphorylated in the human organism to the nucleoside fludarabine (2F-ara-A). After single dose infusion of 25 mg 2F-ara-AMP per m² to cancer 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. Post maximum levels decayed in three disposition phases with an initial half-life of approx. 5 minutes, an intermediate half-life of 1 - 2 hours and a terminal half-life of approx. 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 (V_{ss}) 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 ³H-2F-ara-AMP showed a complete recovery of radio-labelled substances in the urine. Another metabolite, 2F-ara-hypoxanthine, which represents the major metabolite in the dog, was observed in humans only to a minor extent. Individuals with impaired renal function exhibit 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 re-phosphorylated 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 2F-ara-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 approx. 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.

5.3 Preclinical safety data

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).

The results from animal embryotoxicity studies indicated a teratogenic potential of fludarabine phosphate. 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 4.4 and 4.6).

Fludarabine phosphate has been shown to induce chromosomal aberrations in an *in vitro* cytogenetic assay, to cause DNA-damage in a sister chromatid exchange test 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.

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.

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.

6.3 Shelf life

Vial before opening:

2 years

After dilution:

The diluted solution of Fludarabine Phosphate 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 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.

Pack sizes

2 ml vial

5 x 2 ml vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Dilution

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 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).

Inspection prior to use

Only clear, colourless to yellowish solutions without particles should be used. Fludarabine Phosphate should not be used in case of a defective container.

Handling and disposal

Fludarabine Phosphate 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 Fludarabine Phosphate 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 or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER

PA1380/134/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th July 2013
Date of last renewal: 25th April 2018

10 DATE OF REVISION OF THE TEXT

December 2018