Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fludarabine Phosphate 50 mg Powder for Solution for Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg of fludarabine phosphate.

1 ml of reconstituted solutions contains 25 mg of fludarabine phosphate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
A white plug.

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 Powder for Solution for Injection or Infusion 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

Posology

Fludarabine Phosphate Powder for Solution for Injection or Infusion should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

Method of administration

Fludarabine Phosphate Powder for Solution for Injection or Infusion is for intravenous use only.

No cases have been reported in which paravenously administered fludarabine phosphate led to severe local adverse reactions. However, paravenous administration must be avoided.

Adults

The recommended dose of fludarabine phosphate is 25 mg/m^2 body surface area given daily for 5 consecutive days, every 28 days by the intravenous route.
Each vial is to be made up in 2 ml water for injection. Each ml of the resulting solution will contain 25 mg fludarabine phosphate.
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 into 10ml of 0.9% sodium chloride. Alternatively, for infusion the required dose drawn up in a syringe may be diluted into 100ml sodium chloride 9 mg/ml (0.9%) 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 Powder for Solution for Injection or Infusion be administered up to the achievement of response (complete or partial remission, usually 6 cycles). Treatment should then be discontinued.

Special populations

Hepatic Impairment

No data are available concerning the use of Fludarabine Phosphate Powder for Solution for Injection or Infusion in patients with hepatic impairment. In this group of patients, Fludarabine Phosphate Powder for Solution for Injection or Infusion should be used with caution and administered if the perceived benefit outweighs any potential risk.

Renal Impairment

The total body clearance of the principle plasma metabolite, fludarabine (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 kidney 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/min). Therefore, if renal impairment is clinically suspected, or in patients over the age of 65 years, creatinine clearance should be measured. 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. Fludarabine Phosphate Powder for Solution for Injection or Infusion treatment is contraindicated, if creatinine clearance is <30 ml/min (see section 4.3).

Paediatric population

The safety and efficacy of Fludarabine Phosphate Powder for Solution for Injection or Infusion in children has not been established.

Elderly patients

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 over the age of 65 years, creatinine clearance should be measured, see ‘Patients with renal impairment’ and section 4.4.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1 and also:

- in renally impaired patients with creatinine clearance <30 ml/min.
- in patients with decompensated haemolytic anaemia.
- lactation

4.4 Special warnings and precautions for use

- **Mylosuppression**

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) 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 reversible, administration of fludarabine phosphate requires careful haematological monitoring.

Fludarabine Phosphate Powder for Solution for Injection or Infusion is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of haematologic and non-haematologic 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.

- **Autoimmune disorders**

Irrespective of any previous history of autoimmune processes or Coombs test status, life-threatening and sometimes fatal autoimmune phenomena 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 Powder for Solution for Injection or Infusion should be closely monitored for haemolysis.

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

- **Neurotoxicity**

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/m^2/day for 5-7 days) than the recommended dose. In patients treated at doses in the range of the dose recommended for CLL, severe central nervous system toxicity has occurred rarely (coma, seizures and agitation) or uncommonly (confusion).

The effect of chronic administration of Fludarabine Phosphate Powder for Solution for Injection or Infusion on the central nervous system is unknown. However, patients tolerated the recommended dose, in some studies for relatively long term treatment times, (for up to 26 courses of therapy). Patients should be closely observed for signs of neurological side effects.

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

- **Tumour lysis syndrome**

Tumour lysis syndrome associated with fludarabine phosphate treatment has been reported in CLL patients with large tumour burdens. Since Fludarabine Phosphate Powder for Solution for Injection or Infusion 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.

- **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 fludarabine phosphate treated patients. 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 have received, treatment with Fludarabine Phosphate Powder for Solution for Injection or Infusion 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 has been reported in some patients to occur during or after fludarabine phosphate therapy.

- **Impaired state of health**

In patients with impaired state of health, Fludarabine Phosphate Powder for Solution for Injection or Infusion 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.

- **Renal Impairment:**

The total body clearance of the principle metabolite 2-F-ara-A shows a correlation with creatinine, 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 Phosphate Powder for Solution for Injection or Infusion 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 Phosphate Powder for Solution for Injection or Infusion treatment is contraindicated if creatinine clearance is < 30 ml/min (see section 4.3).

- **The elderly**

Since there are limited data for the use of Fludarabine Phosphate Powder for Solution for Injection or Infusion in elderly persons (> 75 years), caution should be exercised with the administration in these patients.

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

- **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 fetal harm (see sections 4.6 and 5.3). Prescribers may only consider the use of fludarabine phosphate, if the potential benefits justify the potential risks to the foetus.

Women should avoid becoming pregnant while on fludarabine phosphate 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 contraceptive measures during and for at least 6 months after cessation of therapy (see section 4.6).

- **Vaccination**

During and after treatment with Fludarabine Phosphate Powder for Solution for Injection or Infusion, vaccination with live vaccines should be avoided.

- **Retreatment options after initial fludarabine phosphate treatment**

A crossover from initial treatment with Fludarabine Phosphate Powder for Solution for Injection or Infusion to chlorambucil for non responders to Fludarabine Phosphate Powder for Solution for Injection or Infusion should be avoided because most patients who have been resistant to fludarabine phosphate have shown resistance to chlorambucil.

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 Powder for Solution for Injection or Infusion in combination with pentostatin is not recommended.

Dipyridamole and other inhibitors of adenosine uptake may reduce the therapeutic efficacy of Fludarabine Phosphate Powder for Solution for Injection or Infusion.

Clinical studies and in vitro experiments showed that during use of fludarabine in combination with cytarabine the intracellular exposure of Ara-CTP (active metabolite of cytarabine) increased in leukaemic 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 embryotoxicity studies in rats and rabbits indicated an embyrolethal 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 fetal harm. Prescribers may only consider the use of fludarabine, if the potential benefits justify the potential risks to the foetus.

- **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).

- **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 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).

4.7 Effects on ability to drive and use machines

Fludarabine has a major influence on the ability to drive and use machines, since *e.g.* fatigue, weakness, visual

disturbances, confusion, agitation and seizures 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 chills, oedema, malaise, peripheral neuropathy, visual disturbance, anorexia, mucositis, stomatitis and skin rashes. Serious opportunistic infections have occurred in patients treated with Fludarabine Phosphate Powder for Solution for Injection or Infusion. 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.

System Organ Class MedDRA	**Very Common** ≥1/10	**Common** ≥ 1/100 to <1/10	**Uncommon** ≥ 1/1000 to <1/100	**Rare** ≥1/10,000 to <1/1000	**Not known**
Infections and infestations	Infections / Opportunistic infections (like latent viral reactivation, e.g. Progressive multifocal leucoencephalopathy, Herpes zoster virus Epstein-Barr-virus), 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, Lymphoproliferative disorder (EBV-associated)	
Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia	Myelosuppression			
Immune system disorders			Autoimmune disorder (including Autoimmune haemolytic anaemia, Evans syndrome, Thrombocytopenic		

			purpura, Acquired haemophilia, Pemphigus)		
Metabolism and nutrition disorders		Anorexia	Tumour lysis syndrome (including Renal failure, Metabolic acidosis, Hyperkalaemia, Hypocalcemia, Hyperuricemia, Haematuria, Urate crystalluria, Hyperphosphatemia)		
Nervous system disorders		Neuropathy peripheral		Coma, Seizures,	Cerebral haemorrhage
Psychiatric disorders			Confusion	Agitation	
Eye disorders		Visual disturbance		Blindness, Optic neuritis, Optic neuropathy	
Cardiac disorders				Heart failure, Arrhythmia	
Respiratory, thoracic and mediastinal disorders	Cough		Pulmonary toxicity (including Pulmonary fibrosis, Pneumonitis, Dyspnoea)		Pulmonary haemorrhage
Gastrointestinal disorders	Vomiting, Diarrhoea, Nausea	Stomatitis	Gastrointestinal haemorrhage,		
Skin and subcutaneous tissue disorders		Rash		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			
Investigations			Pancreatic enzymes abnormal,		

			hepatic enzymes abnormal		

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.

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:

Ireland
HPRA Pharmacovigilence
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 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 Powder for Solution for Injection or Infusion overdose. Treatment consists of drug discontinuation and supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Fludarabine Phosphate Powder for Solution for Injection or Infusion is a water-soluble fluorinated nucleotide analogue of the antiviral agent vidarabine, 9-ß-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase.

Mechanism of action
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.

Pharmacodynamic effects
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 (40 mg/m^2 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 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 responded to Fludarabine Phosphate Powder for Solution for Injection or Infusion have a chance of responding again to Fludarabine Phosphate Powder for Solution for Injection or Infusion monotherapy.

A randomized 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)**

Absorption and Distribution
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 (2F-ara-AMP).

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 25mg 2F-ara-AMP per m^2 to cancer patients for 30 minutes 2F-ara-A reached mean maximum concentrations in the plasma of 3.5 – 3.7µM 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 the 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 approx. 5 minutes, an intermediate half-life of 1-2 hours and a terminal half-life of approx. 20 hours.

Distribution
An interstudy comparison of 2F-ara-A pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 ± 40 ml/min/m^2 (2.2 ± 1.2 ml/min/kg) and a mean volume of distribution (Vss) of 83 ±55 l/m^2 (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 dose indicating a dose linear behaviour.

Occurrence of neutropenia and haematocrit changes indicated that a cytotoxicity of fludarabine phosphate depresses the

haematopoiesis in a dose dependent manner.

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. 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 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 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.

No clear correlation was found between 2F-ara-A pharmacokinetics and treatment efficacy in cancer patients.

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).

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 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 Powder for Solution for Injection or Infusion is associated with a relevant risk of teratogenic effects in humans (see section 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium Hydroxide (for pH adjustment)

6.2 Incompatibilities

In the absence of combatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2 years

In Use:
Fludarabine Phosphate 50 mg Powder for Solution for Injection or Infusion 50mg, following reconstitution with Water for Injection to 25mg/ml, is stable for up to 8 hrs when stored either at 2-8ºC when protected from light or at 25ºC in normal light conditions.

The infusion solution is chemically stable when stored in PVC infusion bags, prepared under full aseptically controlled conditions, for 8 hours when stored either at 2-8ºC protected from light or at 25ºC in normal light conditions.

From a microbiological point of view however, the product should 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 8 hours at 2-8ºC or 8 hours at room temperature.

6.4 Special precautions for storage

Do not store above 25°C

For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3

6.5 Nature and contents of container

10 ml Type I (clear glass) vials with a rubber stopper and plastic flip-off top

Each pack contains 5 vials.

6.6 Special precautions for disposal and other handling

Reconstitution
Fludarabine Phosphate Powder for Solution for Injection or Infusion should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2ml of sterile water for injection, the powder should fully dissolve in 15 seconds or less. Each ml of the resulting solution will contain 25mg of fludarabine

phosphate, 25mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. The pH range for the final product is 7.2 - 8.2.

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.

In clinical studies, the product has been diluted in 100 ml or 125 ml of 5 % dextrose injection or 0.9 % sodium chloride.

Inspection prior to use
Fludarabine Phosphate Powder for Solution for Injection or Infusion should not be used in case of a defective container.

The reconstituted solution is clear and colourless. It should be visually inspected before use.
Only clear and colourless solutions without particles should be used.

Handling and disposal
Fludarabine Phosphate Powder for Solution for Injection or Infusion 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 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.

The medicinal product is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Queensway,
Royal Leamington Spa,
Warwickshire,
CV31 3RW,
UK

8 MARKETING AUTHORISATION NUMBER

PA 0437/061/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th August 2008

Date of last renewal: 15th December 2011

10 DATE OF REVISION OF THE TEXT

August 2015