Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fludarabine Phosphate 50mg 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.

Excipient with known effect:

Each vial of fludarabine phosphate 50 mg powder for solution for injection /infusion contains less than 1 mmol sodium (23 mg), i.e. essentially 'sodium-free'.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection/ infusion.

Sterile lyophilized white or almost white powder or cake.

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

Intravenous administration

Fludarabine must be administered only intravenously.

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

Adults

The recommended dose of fludarabine is 25 mg/m2 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 injections. Each ml of the resulting solution for injection /infusion contains 25 mg fludarabine phosphate (see section 6.6).

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 into 10 ml of sodium chloride 9 mg/ml (0.9%). Alternatively, for infusion,

the required dose drawn up in a syringe may be diluted into 100 ml sodium chloride 9 mg/ml (0.9%) and infused over approximately 30 minutes.

The duration of treatment depends on the treatment success and the tolerability of the drug.

Fludarabine should be administered up to the achievement of best response (complete or partial remission, usually 6 cycles) and then the drug should be discontinued.

Hepatic Impairment

The safety and efficacy have not been studied in patients with hepatic impairment. In this group of patients, fludarabine must 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 (2F-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. Doses should be adjusted for patients with reduced kidney function. If creatinine clearance is between 30 and 70 ml/min, the dose should be reduced by up to 50% and close haematological monitoring should be used to assess toxicity. For further information see section 4.4. Fludarabine treatment is contraindicated, if creatinine clearance is <30 ml/min (see section 4.3).

Paediatric population

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

Elderly patients

Since there are limited data for the use of fludarabine 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 4.4.

Method of administration

For instructions on reconstitution or dilution of the medicinal product before administration, see section 6.6

4.3 Contraindications

Hypersensitivity to the active substance or 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

- **Myelosuppression**

Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine. 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 requires careful haematological monitoring.

Fludarabine 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 must be exercised with fludarabine, when further haematopoietic stem cell sampling is considered.

- **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. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with fludarabine. Patients treated with fludarabine must be closely monitored for haemolysis.

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

The effect of chronic administration of fludarabine on the central nervous system is unknown. However, patients tolerated the recommended dose in some studies for relatively long 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 treatment has been reported in CLL patients with large tumour burdens. Since fludarabine can induce a response as early as the first week of treatment precautions must 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 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 must 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 therapy.

- **Impaired state of health**

In patients with impaired state of health, fludarabine must 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 principal 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 (area under curve) 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 impairment. In patients with moderate impairment of renal function (creatinine clearance between 30 ml/min 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).

- **The elderly**

Since there are limited data for the use of fludarabine 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 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, if the potential benefits justify the potential risks to the foetus.

Women should avoid becoming pregnant while on fludarabine therapy.

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

- **Contraception**

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

- **Vaccination**

During and after treatment with fludarabine, vaccination with live vaccines must be avoided.

- **Retreatment options after initial fludarabine treatment**

A crossover from initial treatment with fludarabine to chlorambucil for non responders to fludarabine should be avoided because most patients who have been resistant to fludarabine have shown resistance to chlorambucil.

Excipients
Each vial of fludarabine phosphate 50 mg powder for solution for injection / infusion contains less than 1 mmol sodium (23 mg), i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pentostatin:

In a clinical investigation using intravenous fludarabine 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 in combination with pentostatin is not recommended.

Dipyridamole:

Dipyridamole and other inhibitors of adenosine uptake may reduce the therapeutic efficacy of fludarabine.

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 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 (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.

- **Lactation**

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 may reduce 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

Based on the experience with the use of Fludara, 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. 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			Lymphoproliferative disorder (EBV−associated)	
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Myelodysplastic syndrome and Acute myeloid leukaemia (mainly associated with prior, concomitant or subsequent treatment with alkylating agents, topoisomerase inhibitors or irradiation)			
Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia	Myelosuppression			
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	Confusion	Coma, Seizures, Agitation	Cerebral haemorrhage
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, Pancreatic enzymes abnormal		
Hepatobiliary disorders			Hepatic enzyme abnormal		
Skin and subcutaneous tissue disorders		Rash		Skin cancer, Necrolysis epidermal toxic (Lyell type), Stevens-Johnson syndrome	
Renal and urinary disorder					Haemorrhagic cystitis
General disorders and administration site conditions	Fever, Fatigue, Weakness,	Oedema, Mucositis, Chills, Malaise			

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

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

4.9 Overdose

Symptoms
High doses of fludarabine 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.

Management
There is no known specific antidote for fludarabine over dosage. 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 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.

Fludarabine 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 (deoxyribonucleotide) 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 (ribonucleic acid) 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.

A phase III trial in patients with previously untreated B-chronic lymphocytic leukaemia comparing treatment with fludarabine vs. chlorambucil (40 mg/m2 q4 weeks) in 195 and 199 patients respectively showed the following outcome: statistically significant higher overall response rates and complete response rates after 1st line treatment with fludarabine 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 group. The median survival of the two patient groups was 56.1 months for fludarabine 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 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 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 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 group than in the chlorambucil group.

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

A randomized trial of fludarabine 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 compared to CAP (45% vs. 26% and 13% vs. 6% respectively); response duration and overall survival were similar with fludarabine and CAP. Within the stipulated treatment period of 6 months the number of deaths was 9 (fludarabine) 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 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 (2F- ara-AMP) in patients with malignant diseases.

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 µM - 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 µM - 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. 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 (Vss) of 83 ± 55 l/m2 (2.4 ± 1.6 l/kg). Data showed a high inter individual 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 depresses the haematopoiesis in a dose dependent manner.

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 2- 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 2F-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 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 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. 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 is associated with a relevant risk of teratogenic effects in humans (see section 4.6).

Fludarabine 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 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, 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 /ml.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium hydroxide (E524) (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

After first opening, the product should be used immediately.

After reconstitution:

The physicochemical stability of the drug product after reconstitution in water for injections has been demonstrated for 24 hours at 25°C ± 2°C/ 60% ± 5%RH and for 7 days at 5°C ± 3°C.

From a microbiological point of view, 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 24 hours at 2ºC to 8ºC.

After dilution:

The infusion solution is chemically stable when stored in infusion bags of 0.9 % sodium chloride solution or 5 % dextrose solution, for 48 hours when stored at 2ºC to 8ºC or 24 hours at 25ºC under 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 24 hours at 2ºC to 8ºC, unless dilution has taken place in a controlled and validated aseptic condition.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

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

6.5 Nature and contents of container

Type-I, 6 ml, clear, moulded glass vials, closed with a 20 mm grey bromobutyl rubber stoppers and sealed with 20 mm green aluminum flip off overseals.

Each pack contains 1 vial.

6.6 Special precautions for disposal and other handling

Reconstitution

Fludarabine must be prepared for parenteral use by aseptically adding sterile water for injections. When reconstituted with 2 ml of sterile water for injections, the powder should fully dissolve in less than 60 seconds. Each ml of the resulting solution will contain 25 mg of fludarabine phosphate, 25 mg 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 into 10 ml of sodium chloride 9 mg/ml (0.9%). Alternatively, for infusion the required dose drawn up in a syringe may be diluted into 100 ml sodium chloride 9 mg/ml (0.9%) or 5% dextrose injection 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.

The dilution compatibility study has been carried out in polyolefin infusion bags.

Inspection prior to use

Fludarabine must 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 must 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 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 product or waste material should be disposed of in

accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Lion Court
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Bordon
Hampshire GU35 0NF
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1422/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 3rd May 2013

10 DATE OF REVISION OF THE TEXT