Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate contains 25 mg fludarabine phosphate.
Each vial of 2 ml contains 50 mg fludarabine phosphate.

Excipient with known effect:
Sodium, less then 1 mmol (23 mg) per vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion.

Fludarabine phosphate 25 mg/ml is a clear, colourless or slightly brownish-yellow solution, essentially free from particles.

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

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 further diluted into 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 be administered up to the achievement of response (usually 6 cycles) and then the drug should be discontinued.

Special populations

Patients with hepatic impairment
No data are available concerning the use of fludarabine in patients with hepatic impairment. In this group of patients, fludarabine should be used with caution and administered if the perceived benefit outweighs any potential risk. Such patients should be monitored closely for excessive toxicity and dosage should be modified or the drug discontinued accordingly. See also section 4.4.

Patients with 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 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 treatment is contraindicated, if creatinine clearance is < 30 ml/min.

Paediatric population
Fludarabine is not recommended for use in children, due to a lack of data on safety and/or efficacy.

Elderly
Since there are limited data for the use of fludarabine in elderly persons (> 75 years), caution should be exercised with the administration of fludarabine in these patients (see also section 4.4).
In patients aged 65 years or older, creatinine clearance should be measured before start of treatment, see “Patients with renal impairment” and section 4.4.

Method of administration

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

It is strongly recommended that fludarabine should be only administered intravenously. No cases have been reported in which paravenously administered fludarabine led to severe local adverse reactions. However, the unintentional paravenous administration must be avoided.

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

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.
- Pregnancy and 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 days) for platelets. Most patients had haematologic impairment at baseline either as a result of disease or as a result of prior myelosuppressive therapy.

Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine phosphate requires careful haematologic monitoring.

Fludarabine phosphate is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of haematologic and 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 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 should be closely monitored for signs of haemolysis.

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

- Neurotoxicity

The effect of chronic administration of fludarabine on the central nervous system is unknown. However, patients tolerated the recommended dose in some studies for relatively long treatment times (for up to 26 courses of therapy). Patients should be closely observed for signs of neurologic effects. When used at high doses in dose-ranging studies in patients with acute leukaemia, intravenous Fludarabine was associated with severe neurologic 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 chronic lymphocytic leukaemia, severe central nervous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion) (see section 4.8).
In postmarketing experience neurotoxicity has been reported to occur earlier or later than in clinical trials.

- Tumour lysis syndrome

Tumour lysis syndrome has been reported in patients with large tumour burdens. Since fludarabine 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 treated patients. Fatal outcome as a consequence of this disease has been reported with a high frequency. Therefore, to minimize the risk of transfusion-associated graft-versus-host disease, patients who require blood transfusion and who are undergoing, or who have received treatment with fludarabine 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 during or after fludarabine therapy.

- Impaired state of health

In patients with impaired state of health, fludarabine 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 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).

- Hepatic impairment

In patients with hepatic impairment fludarabine should be used with caution because it can cause hepatic toxicity. Fludarabine should only be administered if the perceived benefit outweighs any potential risk. Such patients should be monitored closely for excessive toxicity and dosage modified or the drug discontinued accordingly. See also section 4.2.

- Elderly

Since there are limited data for the use of fludarabine in elderly persons (> 75 years), caution should be exercised with the administration of fludarabine in these patients.
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 in children. Therefore, treatment with fludarabine in children is not recommended.

- 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 fetus.
Women should avoid becoming pregnant while on fludarabine therapy.
Women of childbearing potential must be apprised of the potential hazard to the fetus.

- Contraception

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

- Vaccination

During and after treatment with fludarabine vaccination with live vaccines should 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

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In a clinical investigation using fludarabine in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukaemia (<?xml:namespace prefix = st1 ns = "urn:schemas-microsoft-com:office:smarttags" /><st1:stockticker w:st="on">CLL</st1:stockticker>), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine in combination with pentostatin is not recommended.

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. Prescribers may only consider the use of fludarabine, if the potential benefits justify the potential risks to the fetus.

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

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).

Breast-feeding

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).

Fertility

There are no human data on the effect of fludarabine on fertility. In animals, fludarabine has been shown to adversely affect the male reproductive system (see section 5.3).

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 fludarabine, the most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anaemia), infection including pneumonia, cough, fever, fatigue, weakness, nausea, vomiting and diarrhoea. Other commonly reported events include chills, oedema, malaise, peripheral neuropathy, visual disturbance, anorexia, mucositis, stomatitis and skin rash. Serious opportunistic infections have occurred in patients treated with fludarabine. 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** ≥ 1/1,000 to <1/100	**Rare** ≥1/10,000 to <1/1,000	**Not known** cannot be estimated from the available data
Infections and infestations	Infections / Opportunistic infections (like latent viral reactivation, e.g. Progressive multifocal leucoencephalopathy, Herpes zoster virus Epstein-Barr-virus), Pneumonia			Lymphoproliferative disorder (EBV-associated)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Myelodysplastic syndrome and Acute myeloid leukaemia (mainly associated with prior, concomitant or subsequent treatment with alkylating agents, topoisomerase inhibitors or irradiation)			
Blood and lymphatic system disorders	Neutropenia, Anaemia, Thrombocytopenia	Myelosuppression			
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.

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 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 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

Fludarabine Phosphate 25 mg/ml concentrate for solution for injection or infusion 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, <?xml:namespace prefix = st1 ns = "urn:schemas-microsoft-com:office:smarttags" /><st1:stockticker w:st="on">DNA</st1:stockticker> polymerase α/δ and ε, <st1:stockticker w:st="on">DNA</st1:stockticker> primase and <st1:stockticker w:st="on">DNA</st1:stockticker> ligase thereby inhibiting <st1:stockticker w:st="on">DNA</st1:stockticker> 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.

A phase <st1:stockticker w:st="on">III</st1:stockticker> 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 the 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 respond to fludarabine have a chance of responding again to fludarabine monotherapy.
A randomised trial of fludarabine vs. cyclophosphamide, adriamycin (doxorubicin) and prednisone (<st1:stockticker w:st="on">CAP</st1:stockticker>) in 208 patients with <st1:stockticker w:st="on">CLL</st1:stockticker> 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 <st1:stockticker w:st="on">CAP</st1:stockticker> (45% vs. 26% and 13% vs. 6%, respectively); response duration and overall survival were similar with fludarabine and <st1:stockticker w:st="on">CAP</st1:stockticker>. Within the stipulated treatment

period of 6 months the number of deaths was 9 (fludarabine) vs. 4 (<st1:stockticker w:st="on">CAP</st1:stockticker>).
Post-hoc analyses using only data of up to 6 months after start of treatment revealed a difference between survival curves of fludarabine and <st1:stockticker w:st="on">CAP</st1:stockticker> in favour of <st1:stockticker w:st="on">CAP</st1:stockticker> 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, 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 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. 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.

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

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

5.3 Preclinical safety data

Acute and repeat dose toxicology studies in animals showed that the bone marrow, lymphoid organs, gastrointestinal

mucosa, kidneys and the male reproductive organs were the primary target organs of toxicity. Neurotoxicity was seen at high dosages.

Fludarabine phosphate was teratogenic in animals and caused skeletal malformations and external deformities at dosages similar or less than the therapeutic dose.

Genotoxicity studies demonstrated that fludarabine phosphate was negative in gene mutation assays and in the dominant lethal test in male mice, but did induce clastogenic effects in the non-activated chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells and in the *in vivo* mouse micronucleus test.

No carcinogenicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium Hydroxide (E524) for pH adjustment)
Water for Injections

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

Vial before opening
36 months

After dilution
Chemical and physical in-use stability of the solution prepared for injection or infusion has been demonstrated as:

Storage in	Medium	Concentration	Stability for
Non-PVC bag	0.9% sodium chloride	0.3-6 mg/ml	5 days in a refrigerator (2-8 °C) or at ambient temperature/light
	5% glucose	0.3-6 mg/ml	5 days in a refrigerator (2-8 °C) or at ambient temperature/light
Glass bottle	0.9% sodium chloride	0.3-6 mg/ml	5 days in a refrigerator (2-8 °C) or at ambient temperature/light
	5% glucose	0.3 mg/ml	5 days in a refrigerator (2-8 °C) or at ambient temperature/light
		6 mg/ml	5 days in a refrigerator (2-8 °C) or 3 days at ambient temperature/light

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 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.

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

6.5 Nature and contents of container

One Type I glass vial with bromobutyl rubber stopper, aluminium seal and polypropylene snap-cap containing 2 ml of solution.

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

Inspection prior to use
Only clear and colourless solutions without particles should be used. The product should not be used in case of a defective container.

Handling and disposal
Fludarabine 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 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 medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7 MARKETING AUTHORISATION HOLDER

Pharmachemie B.V.
Swensweg 5
2031 RN Haarlem
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 937/6/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd June 2007

Date of last renewal: 20th April 2012

10 DATE OF REVISION OF THE TEXT

September 2016