1. NAME OF THE MEDICINAL PRODUCT

Fludara.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg fludarabine phosphate.

One ml of reconstituted solution contains 25 mg fludarabine phosphate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

White lyophilisate for reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Palliative treatment of patients with CLL refractory to other therapy. Treatment of less malignant Non-Hodgkin lymphoma of stage 3 to 4 in patients who have not responded to standard therapy with at least one alkylating agent or in whom the disease progressed during or after standard therapy. Fludara is indicated for the initial treatment of patients with B- cell chronic lymphocytic leukaemia (CLL) or after first line therapy, in patients with sufficient bone marrow reserves.

First line treatment with Fludara 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 area given daily for 5 consecutive days every 28 days by 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 (see section 6.6).

The required dose (calculated on the basis of the patient's body surface area) of the reconstituted solution is drawn up into a syringe. For intravenous bolus injection this dose is further diluted in 10 ml sodium chloride 9 mg/ml (0.9%). Alternatively, for infusion, the required dose drawn up in a syringe may be diluted in 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.

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

- Patients with renal impairment

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 (see section 4.4).

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

- Patients with hepatic impairment

No data are available concerning the use of Fludara in patients with hepatic impairment. In this group of patients, Fludara should be used with caution.

- Paediatric population

The safety and efficacy of Fludara in children below the age of 18 years have not been established. Therefore, Fludara is not recommended for use in children.

- Older people

Since there are limited data for the use of Fludara in older people (> 75 years), caution should be exercised with the administration of Fludara 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).

Method of administration

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

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

Precautions to be taken before handling the medicinal product.

For instructions on handling and reconstitution 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 sections 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 Fludara. 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 Fludara. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with Fludara. Patients treated with Fludara should be closely monitored for signs of haemolysis.
Discontinuation of therapy with Fludara 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 Fludara 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 Fludara 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 CLL, severe central nervous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion) (see section 4.8).

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

Administration of Fludara can be associated with leukoencephalopathy (LE), acute toxic leukoencephalopathy (ATL) or reversible posterior leukoencephalopathy syndrome (RPLS).
These may occur:

- at the recommended dose
- o when Fludara is given following, or in combination with, medications known to be associated with LE, ATL or RPLS,
- o or when Fludara is given in patients with other risk factors such as cranial or total body irradiation, Hematopoietic Cell Transplantation, Graft versus Host Disease, renal impairment, or hepatic encephalopathy.
- at doses higher than the recommended dose

LE, ATL or RPLS symptoms may include headache, nausea and vomiting, seizures, visual disturbances such as vision loss, altered sensorium, and focal neurological deficits. Additional

effects may include optic neuritis, and papillitis, confusion, somnolence, agitation, paraparesis/ quadriparesis, muscle spasticity and incontinence.
LE/ ATL/ RPLS may be irreversible, life-threatening, or fatal.
Whenever LE, ATL or RPLS is suspected, fludarabine treatment should be stopped. Patients should be monitored and should undergo brain imaging, preferably utilizing MRI. If the diagnosis is confirmed, fludarabine therapy should be permanently discontinued.

Tumour lysis syndrome

Tumour lysis syndrome has been reported in CLL patients with large tumour burdens. Since Fludara 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, and hospitalisation may be recommended for these patients during the first course of treatment.

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 Fludara-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 who have received treatment with Fludara 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 Fludara therapy.

Impaired state of health

In patients with impaired state of health, Fludara 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).
Fludara 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). Fludara treatment is contraindicated if creatinine clearance is < 30ml/min (see section 4.3).

Older people

Since there are limited data for the use of Fludara in older people (> 75 years), caution should be exercised with the administration of Fludara in these patients (see also section 4.2).

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

Pregnancy

Fludara should not be used during pregnancy unless clearly necessary (e.g. life-threatening situation, no alternative safer treatment available without compromising the therapeutic benefit, treatment cannot be avoided). It has the potential to cause foetal harm (see sections 4.6 and 5.3). Prescribers may only consider the use of Fludara, if the potential benefits justify the potential risks to the foetus.

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

Vaccination

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

Retreatment options after initial Fludara treatment

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

Excipients

Each vial Fludara 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

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

Dipyridamole and other inhibitors of adenosine uptake may reduce the therapeutic efficacy of Fludara.
Clinical studies and in vitro experiments showed that during use of Fludara in combination with cytarabine the intracellular peak concentration and intracellular exposure of Ara-CTP (active metabolite of cytarabine) increased in leukemic cells. Plasma concentrations of Ara-C and the elimination rate of Ara-CTP were not affected.

4.6 Pregnancy and lactation

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).

Pregnancy

Pre-clinical data in rats demonstrated a transfer of Fludara and/or metabolites through the placenta. The results from intravenous embryotoxicity studies in rats and rabbits indicated an embryolethal and teratogenic potential at the therapeutic doses (see section 5.3).

There are very limited data of Fludara use in pregnant women in the first trimester:

Fludara 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). Fludara has the potential to cause foetal harm. Prescribers may only consider the use of Fludara 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 phosphate and/or metabolites transfer from maternal blood to milk.

Because of the potential for serious adverse reactions to Fludara in breast-fed infants, Fludara is contraindicated in nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines

Fludara 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

Summary of safety profile

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 rash. Serious opportunistic infections have occurred in patients treated with Fludara. Fatalities as a consequence of serious adverse events have been reported.

Tabulated list of adverse reactions

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 Fludara. The rare adverse reactions were mainly identified from the post-marketing experience.

System Organ Class	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10,000 to <1/1000)**
Infections and infestations	Infections / Opportunistic infections (like latent viral reactivation, e.g. Progressive multifocal leukoencephalopathy, Herpes zoster virus Esptein-Barr-virus), pneumonia			Lympho-proliferative disorder (EBV-associated)
Neoplasms benign,		Myelodysplastic syndrome and		

malignant and unspecified (incl cysts and polyps)		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, Evan's syndrome, Thrombocytopenic purpura, Acquired haemophilia pemphigus)	
Metabolism and nutrition disorders		Anorexia	Tumour lysis syndrome (including renal failure, metabolic acidosis, hyperkalaemia, hypocalcaemia, hyperuricaemia, haematuria, urate crystalluria, hyperphosphataemia)	
Nervous system disorders		Peripheral neuropathy	Confusion	Coma, seizures, agitation
Eye disorders		Visual disturbances		Blindness, optic neuritis, optic neuropathy
Cardiac disorders				Heart failure, arryhthmia
Respiratory, thoracic and	Cough		Pulmonary toxicity	

mediastinal disorders			(including pulmonary fibrosis, pneumonitis, dyspnoea)	
Gastro-intestinal disorders	Vomiting, diarrhoea, nausea	Stomatitis	Gastrointestinal haemorrhage, pancreatic enzymes abnormal	
Hepatobiliary disorders			Hepatic enzymes abnormal	
Skin and subcutaneous tissue disorders		Rash		Skin cancer, necrolysis epidermal toxic (Lyell type) Stevens-Johnson syndrome
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.

Postmarketing experience with frequency unknown:
- Nervous system disorders:

o Cerebral haemorrhage
o Leukoencephalopathy (see section 4.4)
o Acute toxic leukoencephalopathy (see section 4.4)
o Reversible posterior leukoencephalopathy syndrome (RPLS) (see section 4.4)

- Respiratory, thoracic and mediastinal disorders
    - Pulmonary haemorrhage

- Renal and urinary disorder
    - Haemorrhagic cystitis

- Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

High doses of Fludara have been associated with leukoencephalopathy, acute toxic leukoencephalopathy, or reversible posterior leukoencephalopathy syndrome (RPLS). Symptoms may include headache, nausea and vomiting, seizures, visual disturbances such as vision loss, altered sensorium, and focal neurological deficits. Additional effects may include optic neuritis, and papillitis, confusion, somnolence, agitation, paraparesis/ quadriparesis, muscle spasticity, incontinence,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 Fludara overdosage. Treatment consists of drug discontinuation and supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Fludara contains fludarabine phosphate, 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 phosphate is rapidly dephosphorylated to 2F-ara-A which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2F-ara-ATP. This metabolite has been shown to inhibit ribonucleotide reductase, DNA polymerase α/δ and ε, DNA primase and DNA ligase thereby inhibiting DNA synthesis. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occur.

While some aspects of the mechanism of action of 2F-ara-ATP are as yet unclear, it is assumed that effects on DNA, RNA and protein synthesis all contribute to inhibition of cell growth with inhibition of DNA synthesis being the dominant factor. In addition, in vitro studies have shown that exposure of CLL lymphocytes to 2F-ara-A triggers extensive DNA fragmentation and cell death characteristic of apoptosis.

Clinical efficacy and safety

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

Patients who initially respond to Fludara have a chance of responding again to Fludara monotherapy.

A randomised trial of Fludara 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 Fludara compared to CAP (45% vs. 26% and 13% vs. 6%, respectively); response duration and overall survival were similar with Fludara and CAP. Within the stipulated treatment period of 6 months the number of deaths was 9 (Fludara) 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 Fludara 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 and after peroral dosing of fludarabine phosphate (Fludara, 2F-ara-AMP).

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

However, occurrence of neutropenia and haematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses the haematopoiesis in a dose-dependent manner.

Distribution and metabolism

2F-ara-AMP is a water-soluble prodrug of fludarabine (2F-ara-A), which is rapidly and quantitatively dephosphorylated in the human organism to the nucleoside fludarabine (2F-ara-A).

Another metabolite, 2F-ara-hypoxanthine, which represents the major metabolite in the dog, was observed in humans only to a minor extent.

After single dose infusion of 25 mg 2F-ara-AMP per m^2 to CLL 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 approximately 5 minutes, an intermediate half-life of 1 - 2 hours and a terminal half-life of approximately 20 hours.

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 (MVD) of 83 ± 55 l/m^2 (2.4 ± 1.6 l/kg). Data showed a high interindividual variability. After intravenous and peroral administration of fludarabine phosphate 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 behavior.

Elimination

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

Characteristics in patients

Individuals with impaired renal function exhibited 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 leukemic 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 leukemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited a considerable variation with a median peak concentration of approximately 20 µM. 2F-ara-ATP levels in leukemic 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 leukemic lymphocytes showed a linear relationship between extracellular 2F-ara-A exposure (product of 2F-ara-A concentration and duration of incubation) and intracellular 2F-ara-ATP enrichment. 2F-ara-ATP elimination from target cells showed median half-life values of 15 and 23 hours.

5.3 Preclinical safety data

Systemic toxicity

In acute toxicity studies, single doses of fludarabine phosphate produced severe intoxication symptoms or death at dosages about two orders of magnitude above the therapeutic dose. As expected for a cytotoxic compound, the bone marrow, lymphoid organs, gastrointestinal mucosa, kidneys and male gonads were affected. In patients, severe side effects were observed closer to the recommended therapeutic dose (factor 3 to 4) and included severe neurotoxicity partly with lethal outcome (see section 4.9).

Systemic toxicity studies following repeated administration of fludarabine phosphate showed also the expected effects on rapidly proliferating tissues above a threshold dose. The severity of morphological manifestations increased with dose levels and duration of dosing and the observed changes were generally considered to be reversible. In principle, the available experience from the therapeutic use of Fludara points to a comparable toxicological profile in humans, although additional undesirable effects such as neurotoxicity were observed in patients (see section 4.8).

Embryotoxicity

The results from intravenous animal embryotoxicity studies in rats and rabbits indicated an embryoethal and teratogenic potential of fludarabine phosphate as manifested in skeletal malformations, foetal weight loss and post implantation loss. 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 Fludara is associated with a relevant risk of teratogenic effects in humans (see section 4.6).

Genotoxic potential, tumorigenicity

Fludarabine phosphate has been shown, to cause DNA-damage in a sister chromatid exchange test, to induce chromosomal aberrations in an in vitro cytogenetic assay 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 Fludara therapy can exclusively be verified by epidemiological data.

Local tolerance

According to the results from animal experiments following intravenous administration of fludarabine phosphate, no remarkable local irritation has to be expected at the injection site. Even in case of misplaced injections, no relevant local irritation was observed after paravenous, intraarterial, and intramuscular administration of an aqueous solution containing 7.5 mg fludarabine phosphate/ml.

The similarity in nature of the observed lesions in the gastrointestinal tract after intravenous or intragastric dosing in animal experiments supports the assumption that the fludarabine phosphate induced enteritis is a systemic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium hydroxide (to adjust the pH to 7.7).

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial: 3 years.

Reconstituted and diluted solution
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 should not be longer than 24 hours at 2°C to 8 °C or 8 hours at room temperature.

6.4 Special precautions for storage

Store at room temperature, below 30^0C.

For storage conditions of the reconstituted or diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml colorless Type I glass vials containing 50 mg fludarabine phosphate.

Pack size: 5 vials per carton.

6.6 Special precautions for disposal

Reconstitution

Fludara should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2 ml of sterile water for injection, the powder should fully dissolve in 15 seconds or less. 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 in 10 ml sodium chloride 9mg/ml (0.9%). Alternatively, for infusion, the required dose may be diluted in 100 ml sodium chloride 9mg/ml (0.9%) 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 sodium chloride 9mg/ml (0.9%).

Inspection prior to use

The reconstituted solution is clear and colourless. It should be visually inspected before use.

Only clear and colourless solutions without particles should be used. Fludara should not be used in case of a defective container.

- Handling and disposal

Fludara 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 Fludara 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, spillage or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Genzyme Europe BV
The Netherlands

8. LICENSE NUMBER

063 -27- 27774

9. REGISTRATION HOLDER

Sanofi-Aventis Israel ltd. 10 Beni Gaon, POB 8090, Netanya

The format of this leaflet has been determined by the Ministry of Health and the content thereof has been checked and approved at March 2016.