1. NAME OF THE MEDICINAL PRODUCT

Fludarabin "Ebewe" 50 mg/2 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2 ml vial contain 50 mg fludarabine phosphate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion.
A clear, colourless to almost colourless solution.

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.
Fludarabine 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 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 of fludarabine is 25 mg/m^2 body surface given daily for 5 consecutive days (= one cycle) 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 in10 ml of sodium chloride 9 mg/ml (0.9%) solution for injection. Alternatively, for infusion, the required dose may be diluted in 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or in 100 to 125 ml of glucose 5% solution and infused intravenously over a period of 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 medicinal product.
  It is recommended to administer fludarabine until response is achieved (usually after 6 cycles) and then the medicinal product should be discontinued.

- 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.
- 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 must be reduced by up to 50% and close haematological monitoring should be used to assess toxicity (see section 4.4). Fludarabine treatment is

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

- Paediatric population
  Fludarabine is not recommended for use in children below the age of 18 years due to a lack of data on safety and/or efficacy.

- Older people
  Since there are only limited data available concerning the use of fludarabine phosphate in older people (> 75 years), caution should be exercised when fludarabine phosphate is used for these patients.
  In patients over the age of 65 years, 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, unintentional paravenous administration of fludarabine must be avoided.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients,
- Renal impairment with creatinine clearance < 30 ml/min,
- Decompensated haemolytic anaemia,
- Lactation.

4.4 Special warnings and precautions for use

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

Administration of fludarabine phosphate can be associated with leukoencephalopathy (LE), acute toxic leukoencephalopathy (ATL) or reversible posterior leukoencephalopathy syndrome (RPLS).

These may occur:

- at the recommended dose
  - when fludarabine phosphate is given following, or in combination with, medications known to be associated with LE, ATL or RPLS
  - or when fludarabine phosphate 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.

Impaired state of health
In patients with impaired state of health, fludarabine phosphate should be given with caution and after careful risk/benefit consideration. This applies especially for patients with severe impairment of bone marrow function (thrombocytopenia, anaemia, and/or granulocytopenia), immunodeficiency or with a history of opportunistic infection.

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 phosphate must be administered cautiously in patients with renal insufficiency. In patients with moderate impairment of renal function (creatinine clearance between 30 and 70 ml/min), the dose should be reduced by up to 50% and the patient should be monitored closely (see section 4.2).
Fludarabine phosphate treatment is contraindicated if creatinine clearance is < 30 ml/min (see section 4.3).

Myelosuppression
Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a Phase I intravenous study in adult solid tumour patients, the median time to nadir counts was 13 days (range: 3-25 days) for granulocytes and 16 days (range: 2-32 days) for platelets. Most patients had 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 hematopoietic stem cell sampling is considered.

Transfusion-associated graft-versus-host disease
Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) has been observed after transfusion of non-irradiated blood in fludarabine phosphate 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 phosphate should receive irradiated blood only.

Skin cancer
The worsening or flare up of pre-existing skin cancer lesions as well as new onset of skin cancer has

been reported in some patients during or after fludarabine phosphate therapy.

Tumour lysis syndrome
Tumour lysis syndrome has been reported in CLL patients with large tumour burdens. Since fludarabine phosphate can induce a response as early as within 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.

Autoimmune disorders
Irrespective of any previous history of autoimmune processes or Coombs test status, life-threatening and sometimes fatal autoimmune phenomena (e.g. autoimmune haemolytic anaemia, autoimmune thrombocytopenia, thrombocytopenic purpura, pemphigus, Evans' syndrome) have been reported to occur during or after treatment with fludarabine phosphate. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with fludarabine phosphate. Patients treated with fludarabine phosphate should be closely monitored for signs of haemolysis.
Discontinuation of therapy with fludarabine phosphate is recommended in case of haemolysis. Blood transfusions (irradiated, see above) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.

Older people
Since there are limited data for the use of fludarabine phosphate in elderly persons (> 75 years), caution should be exercised with the administration of fludarabine phosphate in these patients (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
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 effective contraceptive measures during and at least for 6 months after cessation of therapy (see section 4.6).

Vaccination
During and after treatment with fludarabine phosphate vaccination with live vaccines should be avoided.

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

Fludarabine "Ebewe" 50 mg/2 ml contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 45 mg (average dose), that is to say essentially ‘sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

In a clinical investigation using intravenous fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukaemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of fludarabine phosphate in

combination with pentostatin is not recommended.
Dipyridamole and other inhibitors of adenosine uptake may reduce the therapeutic efficacy of fludarabine phosphate.
Clinical studies and in vitro experiments showed that during use of fludarabine phosphate 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-CTP and the elimination rate of Ara-CTP were not affected.

4.6 Fertility, 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
Preclinical data in rats demonstrated a transfer of fludarabine and/or metabolites through the placenta. The results from intravenous embryotoxicity studies in rats and rabbits indicated an embyrolethal and teratogenic potential at the therapeutic doses (see section 5.3).
There are very limited data of fludarabine use in pregnant women in the first trimester.
Fludarabine should not be used during pregnancy unless clearly necessary (e.g. life- threatening situation, no alternative safer treatment available without compromising the therapeutic benefit, treatment cannot be avoided). Fludarabine has the potential to cause fetal harm. Prescribers may only consider the use of fludarabine, if the potential benefits justify the potential risks to the foetus.

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).

4.7 Effects on ability to drive and use machines

Fludarabine phosphate 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 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.

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

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)

System Organ Class	Very Common	Common	Uncommon	Rare
Infections and infestations	Infections / Opportunistic infections (like latent viral reactivation, e.g. progressive multifocal leucoencephalopathy, herpes zoster virus, Epstein-Barr-virus), pneumonia			Lymphoproliferative disorder associated)

System Organ Class MedDRA	Very Common	Common	Uncommon	Rare
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, thrombo-cytopenia	Myelo-suppression		
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
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)	
Gastro-intestinal disorders	Vomiting, diarrhoea, nausea	Stomatitis	Gastrointestinal haemorrhage, pancreatic enzymes abnormal	

System Organ Class MedDRA	Very Common	Common	Uncommon	Rare
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				
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

o Pulmonary haemorrhage

- Renal and urinary disorder

o 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 via the following link: https://sideeffects.health.gov.il/

4.9 Overdose

High doses of fludarabine phosphate 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 specific antidote for fludarabine phosphate overdosage. Treatment consists of drug discontinuation and supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, ATC code: L01B B05

Mechanism of action
Fludarabine phosphate contains fludarabine phosphate (2F-Ara-AMP), a water-soluble fluorinated nucleotide analogue of the antiviral agent vidarabine (Ara-A, 9-ß-D-arabinofuranosyladenine) 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 intracellularly phosphorylated by deoxycytidine kinase to active triphosphate, 2F-ara-ATP. This metabolite inhibits ribonucleotide reductase, DNA polymerase α/β and ε, DNA primase and DNA ligase thereby preventing 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 believed that effects on DNA, RNA and proteinsynthesis all contribute to the 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 apoptosis with extensive DNA fragmentation.

Clinical efficacy and safety
In a phase-III-study including patients with previously untreated B-cell-CLL, 195 patients were treated with fludarabine and 199 patients with chlorambucil (40 mg/m^2, repeated every 4 weeks).

The overall remission rate and the rate of complete remissions was statistically significant higher after first line treatment with fludarabine in comparison to chlorambucil 61% versus 37.6% and 19% versus 3.4%, respectively. The duration of remission (19 months versus 12.2 months) and time to progression (17 versus 13.2 months) were statistically significant longer with fludarabine treatment than with chlorambucil. Median survival was 56.1 months with fludarabine phosphate and 55.1 months with chlorambucil, a non-significant difference was also shown with performance status. The incidence of toxicities was comparable (89.7% with fludarabine phosphate, 89.9% with chlorambucil). Overall hematological toxicities were equally frequent, but a decrease of the counts of leucocytes and of lymphocytes was significantly more frequent with fludarabine phosphate than with chloramucil ($p = 0.0054$ and 0.0240, respectively). Nausea, vomiting and diarhoea was significantly less frequent with fludarabine phosphate than with chlorambucil ($p < 0.0001$, $p < 0.0001$, $p = 0.0489$, respectively).

Also, liver toxicities were reported for significantly ($p = 0.0487$) less patients in the fludarabine phosphate arm than in the chlorambucil arm.

Patients who initially respond to fludarabine phosphate have a good chance of responding again to fludarabine phosphate monotherapy.

A randomized study comparing fludarabine phosphate with a combination of cyclophosphamide plus adriamycin and prednisolon (CAP) in 208 patients with CLL (Binet stage B and C) showed in a subgroup of 103 pretreated patients the following results: The overall response rate and the number of complete remissions were higher with fludarabine phosphate compared to CAP (45% vs. 26% and 13% vs. 6%, respectively); response duration and overall survival were similar with fludarabine phosphate and CAP. Within the stipulated treatment period of 6 months the number of deaths was 9 (fludarabine phosphate) vs. 4 (CAP).

Post-hoc analyses using data of up to 6 months after start of treatment revealed a difference between survival curves of fludarabine phosphate and CAP in favour of CAP in the subgroup of pre-treated Binet stage C patients.

5.2 Pharmacokinetic properties

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

The pharmacokinetic properties of fludarabine phosphate were investigated after intravenous bolus injection and after short and long term intravenous infusion of fludarabine phosphate (2F-ara-AMP) in patients with malignant diseases.

Distribution and Biotransformation
2F-ara-AMP is a water-soluble prodrug, which is rapidly and quantitatively dephosphorylated in the human organism to the nucleoside fludarabine (2F-ara-A). After cancer patients had received a single infusion of 25 mg 2F-ara-AMP per m² to over 30 minutes, 2F-ara-A reached mean maximum concentrations in the plasma of 3.5-3.7µM at the end of the infusion. Corresponding 2F-ara-A levels after the fifth dose showed a moderate accumulation with mean maximum levels of 4.4-4.8µM at the end of the infusion. During a 5-day treatment period, 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 ruled out. Post maximum levels of 2F-ara-A were reduced 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 inter-study comparison of 2F-ara-A pharmacokinetics resulted in a mean overall 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 dosage, whereas half-lives, plasma clearance and volumes of distribution remained constantly dose independent, indicating a dose linear behaviour.

Occurrence of neutropenia and haematocrit changes indicated that cytotoxicity of fludarabine phosphate causes dose dependent haematopoiesis inhibition.

Elimination
The main pathway of 2F-ara-A elimination leads via the kidneys. 40 to 60% of the administered IV dose was excreted in the urine. Mass balance studies in laboratory animals with ^{3}H-2F-ara-AMP showed that the radio-tagged substances were completely excreted in the urine. 2F-ara-hypoxanthine, which is the major metabolite in dogs, was observed in humans only in small amounts. Since patients with impaired renal function have a reduced total body clearance of 2F-ara-A, dose reduction is required in these cases. In vitro studies with human plasma proteins showed no pronounced tendency of 2F-ara-A protein binding.

Cellular pharmacokinetics of fludarabine triphosphate

2F-ara-A is actively absorbed into leukemic cells, whereupon it is rephosphorylated to mono- and diphosphate and subsequently to triphosphate. Fludarabine triphosphate, 2F-ara-ATP, is the major intracellular metabolite and the only one known to have cytotoxic activity. Maximum 2F-ara-ATP levels in leukemic lymphocytes of CLL patients were observed approx. 4 hours after application and exhibited a considerable variation around a median peak concentration of approx. 20µM. 2F-ara-ATP levels in leukemic cells were considerably higher than maximum 2F-ara-A plasma levels indicating an accumulation in the target cells. In vitro incubation of leukemic lymphocytes showed a linear relationship between extracellular 2F-ara-A exposure (product of 2F-ara-A concentration and incubation time) 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.

However, based on the mechanism of action and the results of the mutagenicity tests, a tumorigenic potential is suspected for fludarabine phosphate.

No carcinogenicity studies have been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate-dihydrate,
Sodium hydroxide,
Water for injection.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

As packaged for sale:
The expiry date of the product is indicated on the packaging materials.

Shelf life after dilution:
Infusion solutions detailed in section 6.6 are physically and chemically stable for at least 28 days when stored in a refrigerator (2°C - 8°C) with protection from light and at room temperature (20°C - 25°C) with and without protection from 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 no be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

As packaged for sale:
Store in a refrigerator (2°C – 8°C).

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

6.5 Nature and contents of container

Colorless type I glass vial with grey fluoropolymer coated chlorobutyl rubber stopper.

Pack sizes: 1 x 2 ml vial.

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 sodium chloride 9 mg/ml (0.9%) solution for injection. Alternatively, for infusion, the required dose may be diluted in 100 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or in 100 to 125 ml of glucose 5% solution and infused over approximately 30 minutes.

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
Pregnant women should be excluded from handling fludarabine phosphate. The Regulations concerning proper handling and disposal must be followed considering guidelines for proper handling and disposal of cytotoxic medicinal products. Any spilled or unused material may be eliminated by incineration.

Caution should be exercised during handling and preparation of fludarabine phosphate solution. The use of protective gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution comes in contact with skin or mucous membranes, the affected area should be cleaned thoroughly with soap and water.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND IMPORTER

Novartis Israel Ltd.,
P.O.Box 7126,
Tel Aviv, Israel

8. MARKETING AUTHORISATION NUMBER(S)

136 44 31351 00

Revised in June 2021 according to MOH guidelines