1. NAME OF THE MEDICINAL PRODUCT

Fludarabin "Ebewe" 25mg/ml solution for injection/concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1ml contains 25mg fludarabine phosphate as active ingredient.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/concentrate for solution for infusion

Product description: clear, colourless or almost colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Chronic lymphocytic leukemia (CLL) of B-cell type patients with sufficient bone marrow function.

First line treatment or second line treatment of patients with sufficient bone marrow function. First line treatment is indicated only in later stages (Rai III/IV, Binet C) or in earlier stages if disease related symptoms make treatment desirable.

4.2. Posology and method of administration

Fludarabin "Ebewe" should be administered under the supervision of a physician with experience in oncology.

It is strongly recommended that Fludarabin "Ebewe" should be only administered intravenously. No cases have been reported in which relevant local irritation was observed after paravenous administration. However, unintentional paravenous administration of Fludarabin "Ebewe" must be avoided.

- Adults

The usual starting dose of Fludarabin "Ebewe" is 25mg/m^2/day administered intravenously for 5 days (= one cycle) every 28 days.

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 in10ml of sodium chloride solution 0.9%. Alternatively, the required dose may be diluted in 100ml of sodium chloride solution 0.9% and infused intravenously over a period of approximately 30 minutes.

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 to administer Fludarabin "Ebewe" until response is achieved (usually after 6 cycles) and then the drug should be discontinued.

- Patients with decreased liver function

No data are available concerning the use of Fludarabin "Ebewe" in patients with hepatic impairment. In this group of patients, Fludarabin "Ebewe" should be used with caution and administered only if expected benefits outweigh potential risks.

- Patients with decreased renal function

Total body clearance of the main plasma metabolite 2F-ara-A correlates with the creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. In patients with reduced kidney function an increased exposure (AUC of 2F-ara-A) was observed. Limited clinical data are available in patients with impaired renal function (creatinine clearance below 70ml/min). Therefore, in patients where renal impairment is clinically suspected, or in patients over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70ml/min, the dose must be reduced by up to 50% and close haematological monitoring should be used to assess toxicity. Fludarabin "Ebewe" treatment is contraindicated, if creatinine clearance is below 30ml/min.

- Children

The safety and effectiveness of Fludarabin "Ebewe" in children has not been established.

4.3. Contraindications

Fludarabine phosphate is contraindicated

in patients who are hypersensitive to the active substance or to any of the product's excipients,

- in patients with impaired renal function and creatinine clearance below 30ml/min,
- in patients with decompensated haemolytic anaemia,
- during pregnancy and lactation.

4.4. Special warnings and precautions for use

When fludarabine phosphate was used at high doses in dose-ranging studies in patients with acute leukaemia, severe neurological effects including blindness, coma, and death occurred. This severe central nervous system toxicity was observed in 36% of patients treated with intravenous doses approximately four times greater than the dose recommended for treatment of CLL (96mg/m^2/day for 5–7 days). 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 occasionally (confusion). Patients should be closely monitored for signs of neurological side effects.

The effects of chronic administration of fludarabine phosphate on the central nervous system are unknown. However, patients tolerate the recommended dose, in some studies even over a relatively long treatment period of up to 26 therapy cycles.

In patients with poor performance status fludarabine phosphate should only be given with caution and after careful risk/benefit consideration. This applies especially to patients with severe impairment of bone marrow function (thrombocytopenia, anaemia, and/or granulocytopenia), with immunodeficiency or with a history of opportunistic infection.

Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a Phase I study in patients with solid tumours, the median time to nadir counts was 13 days (range: 3–25 days) for granulocytes and 16 days (range: 2–32) for platelets. Most patients presented with haematological impairment at baseline either as a result of underlying diseases or as a result of previous myelosuppressive therapy. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine phosphate requires careful haematological monitoring.

Fludarabine phosphate is a potent antineoplastic agent which may have significant toxic side effects. Patients undergoing therapy should be closely examined for signs of haematological and non-haematological toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anaemia, neutropenia, and thrombocytopenia.

As with other cytotoxics, caution should be exercised when fludarabine phosphate is used and when stem cell sampling in the further course of treatment is considered.

Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) was observed after transfusion of non-irradiated blood in patients with fludarabine phosphate. Fatal outcome as a consequence of this disease has been reported very often. Therefore, patients who require blood transfusion prior to or after treatment with fludarabine phosphate should receive irradiated blood only.

Reversible worsening or flare up of pre-existing skin cancer lesions has been reported in some patients to occur during or after treatment with fludarabine phosphate.

Tumour lysis syndrome associated with fludarabine phosphate treatment has been reported in CLL patients with large tumour masses. Since fludarabine phosphate may 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.

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 when being treated with fludarabine phosphate, had recurrent haemolysis after fludarabine phosphate re-exposure. Patients treated with fludarabine phosphate should be closely monitored for haemolysis.

Patients undergoing treatment with fludarabine phosphate should be closely monitored for signs of autoimmune haemolytic anaemia (decline in haemoglobin linked with haemolysis and positive Coombs test). Discontinuation of therapy with fludarabine phosphate is recommended in case of haemolysis. Blood transfusions (irradiated, see above) and adrenocorticoids are common treatment measures for autoimmune haemolytic anaemia.

Since there is only limited data available concerning the use of fludarabine phosphate in elderly persons (> 75 years), caution should be exercised when fludarabine phosphate is used for these patients.

Since there is only limited data available concerning the treatment of children with fludarabine phosphate, its administration is not recommended.

Woman in the childbearing age or men have to use contraceptive measures during and 6 months after treatment. During and after treatment with fludarabine phosphate vaccination with live vaccines should be avoided.

Patients resistant to fludarabine phosphate should not be treated with chlorambucil because these patients are expected to be resistant to chlorambucil too.

4.5. Interaction with other medicinal products and other forms of interaction

In a clinical investigation using 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.

The therapeutic efficacy of fludarabine phosphate may be reduced by dipyridamole and other inhibitors of the adenosine uptake.

A pharmacokinetic drug interaction was observed in CLL and AML (acute myeloid leukaemia) patients during combination therapy with fludarabine phosphate and Ara-C. Clinical and in vitro studies with cancer cell lines demonstrated elevated intracellular Ara-CTP levels in leukemic cells after fludarabine phosphate administration and subsequent Ara-C treatment. This applied to intracellular peak concentrations as well as to total intracellular exposure (AUC). Plasma concentrations of Ara-C and the elimination rate of Ara-CTP were not affected.

4.6. Pregnancy and lactation

Pregnancy

Fludarabine phosphate must not be used during pregnancy.

Women of child-bearing potential should be advised to avoid becoming pregnant and to inform the treating physician immediately in case that this should occur.

Only very limited experience in humans is available to support the findings of embryotoxicity studies in animals demonstrating an embryotoxic and/or teratogenic potential at the therapeutic dose. Preclinical data in rats demonstrated a transfer of fludarabine phosphate and/or its metabolites through the foeto-placental barrier.

Lactation

Breast-feeding must be discontinued for the duration of fludarabine phosphate therapy.

It is not known whether fludarabine phosphate is excxretred in human milk.

However, preclinical data indicate that fludarabine phosphate and/or metabolites transfer from maternal blood to breast milk.

4.7. Effects on ability to drive and use machines

The effects of fludarabine phosphate treatment on the patient's ability to drive or operate machinery have not been studied.

4.8. Undesirable effects

The most common side effects include myelosuppression (neutropenia, thrombocytopenia, and anaemia), infections including pneumonia, fever, nausea, vomiting and diarrhoea. Other commonly reported side effects include fatigue, weakness, stomatitis, malaise, anorexia, oedema, chills, peripheral neuropathy, visual disturbances and skin rashes. Severe opportunistic infections have occurred in patients treated with fludarabine phosphate. Mortality as a consequence of serious adverse events has been reported.

The most frequently reported adverse events and reactions, which are more likely to be related to the drug, are listed below according to body system regardless of their seriousness. Their frequencies (common ≥ 1%, uncommon ≥ 0.1% and < 1%) are based on clinical trial data regardless of the causal relationship with fludarabine phosphate treatment. Rare side effects (< 0.1%) were mainly identified spontaneously.

General disorders and administration site conditions

Infections, fever, fatigue, weakness, malaise, and chills have been commonly reported.

Blood and lymphatic system disorders

Haematological events (neutropenia, thrombocytopenia, and anaemia) have been reported in the majority of patients treated with fludarabine phosphate. Myelosuppression may be severe and cumulative. Long-term reduction of T-lymphocyte levels caused by fludarabine phosphate may lead to an increased risk of opportunistic infections, including those related to latent viral reactivation, e.g. Herpes zoster, Epstein-Barr Virus (EBV) or progressive multi-focal leucoencephalopathy (see section 4.4). Progression of EBV-infection/reactivation into EBV-associated lymphoproliferative disorders has been observed in immunocompromised patients.

In rare cases, the occurrence of myelodysplastic syndrome (MDS) has been described in patients treated with fludarabine phosphate. The majority of these patients also received previous, concomitant, or subsequent treatment with alkylating agents or irradiation. Mono-therapy with fludarabine phosphate has not been associated with an increased risk for the development of MDS.

Occasionally, clinically significant autoimmune phenomena have been reported to occur (see section 4.4).

Metabolism and nutrition disorders

Occasionally, tumour lysis syndromes have been reported in patients treated with fludarabine phosphate. This complication may include hyperuricaemia, hyperphosphataemia, hypocalcaemia, metabolic acidosis, hyperkalaemia, haematuria, urate crystalluria, and renal failure. The onset of this syndrome may be accompanied by hip and flank pain and haematuria.

Oedemas have been commonly reported.

Occasionally, changes in hepatic and pancreatic enzyme levels are observed.

Nervous system disorders

Peripheral neuropathy has been frequently observed. Occasionally, confusion can be observed. Coma, agitation, and seizures have rarely occurred.

Eye disorders

Visual disturbances are commonly reported events in patients treated with fludarabine phosphate. In rare cases, optic neuritis, optic neuropathy and blindness have occurred.

Respiratory, thoracic and mediastinal disorders

Pneumonia commonly occurs in association with fludarabine phosphate treatment. Pulmonary hypersensitivity reactions to fludarabine phosphate (pulmonary infiltrates/pneumonitis/fibrosis), associated with dyspnoea and cough, have been occasionally observed.

Gastrointestinal disorders

Gastrointestinal disturbances such as nausea and vomiting, diarrhoea, stomatitis, and loss of appetite are common side effects. Gastrointestinal bleeding, mainly related to

thrombocytopenia has been occasionally reported in patients treated with fludarabine phosphate.

Cardiac disorders

In rare cases, heart insufficiency and arrhythmia have been reported in patients treated with fludarabine phosphate.

Renal and urinary disorders

Rare cases of haemorrhagic cystitis have been reported.

Skin and subcutaneous tissue disorders

Skin rashes have been commonly reported in patients treated with fludarabine phosphate. In rare cases a Stevens-Johnson syndrome or a toxic epidermal necrolysis (Lyell's syndrome) may develop.

4.9. Overdose

High doses of fludarabine phosphate are considered to be associated with an irreversible central nervous system toxicity characterised by delayed blindness, coma, and death. High doses may also lead to severe thrombocytopenia and neutropenia due to bone marrow suppression. There is no specific antidote known against fludarabine phosphate overdosage. Treatment consists of drug discontinuation and supportive measures.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents

ATC Code: L01B B05

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.

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

The overall remission rate and the rate of complete remissions was 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 longer with fludarabine treatment than with chlorambucil. Median survival was 56.1 months with fludarabine phosphate and 55.1 months with chlorambucil. Tolerability of both medications was also not significantly different. 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.

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 25mg 2F-ara-AMP per m^2 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 ± 40ml/min/m^2 (2.2 ± 1.2ml/min/kg) and a mean volume of distribution (Vss) of 83 ± 55l/m^2 (2.4 ± 1.6l/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.

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

In single dose acute toxicity tests of fludarabine phosphate occur severe toxicity and death after doses, which are two orders of magnitude higher than therapeutic doses. As expected for a cytotoxic compound, toxicity predominantly affects bone marrow, lymphoid organs, gastrointestinal mucosa, kidneys, and male gonads. In patients, severe side effects were observed even at doses that were significantly closer to the recommended therapeutic dose (factor 3 to 4). In such cases neurotoxic effects occurred which were partly fatal (see section 4.9).

Systemic tolerability studies using repeated administration of fludarabine phosphate above a threshold dose also showed expected effects on tissues with high cell division rates. The severity of morphological changes increased with dose levels and duration of treatment and the observed changes were generally considered to be reversible. In principle, the experience gathered during therapeutic use of fludarabine phosphate indicates a comparable toxicological profile in humans, although additional undesirable effects such as neurotoxicity were observed in patients (see section 4.8).

The results from animal embryotoxicity studies suggest a teratogenic potential of fludarabine phosphate. In view of the small safety margin between teratogenic doses in animals and human therapeutic dose as well as in analogy to other antimetabolites, which are assumed to interfere with the process of embryonic cell differentiation, the therapeutic use of fludarabine phosphate must be considered to be associated with a significant risk of teratogenic effects in humans (see section 4.6).

Fludarabine phosphate has been shown to induce chromosomal aberrations in an in vitro cytogenetic assay, to cause DNA-damage in a sister chromatid exchange test and to increase the rate of micronuclei in the mouse micronucleus test in vivo, but was negative in gene mutation assays and in the dominant lethal test in male mice. Thus, the mutagenic potential was demonstrated in somatic cells but could not be shown in germ cells.

The mechanism of action of fludarabine phosphate on a DNA-level and the mutagenicity test results form the basis for the suspicion of a tumorigenic potential. No specific tumorigenicity studies in animals have been conducted, because the suspicion of an increased risk of secondary tumours due to therapy with fludarabine phosphate can only be verified with the help of epidemiological data.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Fludarabin "Ebewe" vials contain disodium phosphate dihydrate, sodium hydroxide and water for injection as constituents in addition to fludarabine.

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:

24 months.

Shelf life after dilution:

Infusion solutions cited above are physically and chemically stable for at least 28 days when stored in a refrigerator (2–8°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 of the diluted medicinal product, see section 6.3

6.5. Nature and contents of container

Clear type I glass vial with rubber stopper.
1 vial containing 50mg/2ml fludarabine phosphate.

6.6. Special precautions for disposal and other handling

Fludarabine phosphate should be prepared for parenteral administration under aseptical conditions adding sterile water for injection.

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

Handling and disposal:

Pregnant women should be excluded from handling fludarabine phosphate. Die Regulations concerning proper handling and disposal must be followed considering guidelines for proper handling and disposal of cytotoxic drugs. 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. Exposure by inhalation of dry substance powder must be avoided.

7. Manufacturer

EBEWE Pharma Ges.m.b.H. Nfg. KG
A-4866 Unterach
AUSTRIA

8. DATE OF REVISION OF THE TEXT

November 2006