NEW ZEALAND DATA SHEET
FLUDARABINE EBEWE (FLUDARABINE PHOSPHATE) SOLUTION FOR INJECTION

1. PRODUCT NAME

Fludarabine phosphate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of FLUDARABINE EBEWE contains 50 mg of the active ingredient fludarabine phosphate.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Fludarabine Ebewe solution for injection.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

FLUDARABINE EBEWE is indicated for the treatment of B-cell chronic lymphocytic leukaemia.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults

The recommended dose is 25 mg/m^2 body surface given daily for 5 consecutive days every 28 days by the intravenous route. Each vial contains 25 mg fludarabine phosphate per mL (50 mg in 2 mL).

The required dose (calculated on the basis of the patient's body surface) is drawn up into a syringe. For intravenous bolus injection, this dose is further diluted into 10 mL physiological saline. Alternately, the required dose drawn up in a syringe may be diluted into 100 mL physiological saline and infused over approximately 30 minutes.

The duration of treatment depends on the treatment success and the tolerability of the medicine. FLUDARABINE EBEWE should be administered up to achievement of best response (complete or partial remission, usually 6 cycles) and then it should be discontinued.

Toxicity

Dosage may be decreased or delayed based on evidence of haematological or non-haematological toxicity. Physicians should consider delaying or discontinuing the medicine if toxicity occurs.

Retreatment Options after Initial FLUDARABINE EBEWE Treatment

Patients who primarily respond to FLUDARABINE EBEWE have a good chance of responding again to FLUDARABINE EBEWE monotherapy. A crossover from initial treatment with FLUDARABINE EBEWE to chlorambucil for non-responders to FLUDARABINE EBEWE should be avoided. In a clinical trial, 46 subjects who failed initial

fludarabine therapy were treated with chlorambucil 40 mg/m^2 every 28 days. Only one subject (2%) achieved a partial response.

Method of administration

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

It is strongly recommended that FLUDARABINE EBEWE should only be administered intravenously. Paravenous administration must be avoided.

Product is for single use in one patient only. Discard any residue.

Dosage adjustment in:

- renal impairment

Dosage reduction is required in renally impaired patients. Refer to Sections 5.2 Pharmacokinetic properties/ Impaired Renal Function and 4.4 Special warnings and precautions for use / Use in Specialised Groups.

- Impaired state of health

A number of clinical settings may predispose to increased toxicity from FLUDARABINE EBEWE. These include advanced age; renal insufficiency and bone marrow impairment (see Section 4.4 Special warnings and precautions for use/ Use in Specialised Groups, Impaired State of Health). Such patients should be monitored closely for excessive toxicity and the dose modified accordingly.

4.3. CONTRAINDICATIONS

FLUDARABINE EBEWE is contraindicated in those patients who are hypersensitive to this medicine or its components, in renally impaired patients with creatinine clearance < 30 mL/min and in patients with decompensated haemolytic anaemia.

FLUDARABINE EBEWE is contraindicated during pregnancy and lactation.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Neurotoxicity

When used at high doses in dose-ranging studies in patients with acute leukaemia, fludarabine phosphate was associated with severe neurologic effects, including blindness, coma and death. This severe central nervous system toxicity occurred in 36% of patients treated intravenously with doses approximately four times greater (96 mg/m^2/day for 5 - 7 days) than the dose recommended for treatment of CLL. 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).

In postmarketing experience, neurotoxicity has also been reported to occur earlier or later than in clinical trials, with a latency ranging from 7 to 225 days after the last dose of fludarabine phosphate.

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).

Patients should be closely observed for signs of neurologic effects.

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,
    - When fludarabine phosphate is given to patients with other risk factors such as previous exposure to 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. Treating physicians should diagnose and monitor the patient with appropriate techniques (ideally brain imaging, MRI etc.).

Myelosuppression

Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a Phase I study in solid tumour patients, the median time to nadir counts was 13 days (range 3 - 25 days) for granulocytes and 16 days (range 2 - 32) for platelets. Most patients had haematologic impairment at baseline either as a result of disease or as a result of prior myelosuppressive therapy. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine phosphate requires careful haematological 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. In such cases, as a general rule, the dose of myelosuppressive agents should be reduced or the dosage interval extended.

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 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.

Disease Progression

Disease progression and transformation (e.g. Richter's syndrome) have been commonly reported in CLL patients.

Transfusion Associated Graft-versus-Host Disease

Transfusion-associated graft-versus-host disease 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, 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 FLUDARABINE EBEWE should receive irradiated blood only.

Skin Cancer Lesions

The worsening or flare up of pre-existing skin cancer lesions as well as new onset of skin cancer has been reported in patients during or after fludarabine phosphate therapy.

Tumour Lysis Syndrome

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

Autoimmune Phenomena

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 undergoing treatment with FLUDARABINE EBEWE should be closely monitored for signs of haemolysis. Discontinuation of therapy with FLUDARABINE EBEWE is recommended in case of haemolysis. Blood transfusion (irradiated) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.

Use in Specialised Groups

Impaired state of health

Patients who have advanced stage disease, hypoalbuminaemia, reduced platelet count or haemoglobin levels, white cell count above 50 x 10^9/L, significant hepatic or spleen enlargement, extensive prior therapy or poor performance status are at risk of serious and sometimes fatal toxicity during the first 6 months of treatment.

Fludarabine treatment may be associated with a spectrum of infections different from those seen with neutropenia from standard chemotherapy medicines. Prophylactic treatment should

be considered in patients at increased risk of developing opportunistic infections, which include, but are not limited to, pneumocytis, fungi and herpes virus infections.

The dose of 25 mg/m^2/day for 5 days by intravenous infusion may be greater than needed in some patients, especially those at risk, and consideration should be given to using a lower dose in such patients.

Vaccination

During and after treatment with FLUDARABINE EBEWE, vaccination with live vaccines should be avoided.

Use in hepatic impairment

No data are available concerning the use of FLUDARABINE EBEWE in patients with hepatic impairment. In this group of patients, FLUDARABINE EBEWE should be used with caution, and administered if the potential benefit outweighs any potential risk.

Use in renal impairment

There are limited data in dosing of patients with renal insufficiency. Careful monitoring for haematological toxicity is required and possible dose reductions of FLUDARABINE EBEWE in patients with renal impairment, patients with depressed white cell count and platelet counts, or patients with infection or bleeding may be required.

The total body clearance of 2-fluoro-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). Limited clinical data are available in patients with impairment of renal function (creatinine clearance below 70 mL/min). FLUDARABINE EBEWE 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 in proportion to the reduced creatinine clearance and close haematological monitoring should be used to assess toxicity. FLUDARABINE EBEWE treatment is contraindicated if creatinine clearance is < 30 mL/min.

Use in the elderly

Since there are limited data for the use of FLUDARABINE EBEWE in elderly persons (> 75 years), caution should be exercised with the administration of FLUDARABINE EBEWE in these patients. In patients aged 65 years or older, creatinine clearance should be measured before start of treatment.

Paediatric use

The safety and effectiveness of FLUDARABINE EBEWE in children has not been established. Therefore, treatment with fludarabine phosphate in children and adolescents is not recommended.

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 EBEWE in combination with pentostatin is not recommended.

A pharmacokinetic interaction was observed in AML patients during combination therapy with fludarabine phosphate and Ara-C. Clinical studies and *in vitro* experiments with cancer cell lines demonstrated elevated intracellular Ara-CTP levels in combination with fludarabine phosphate treatment.

Dipyrimadole and other inhibitors of adenosine uptake may reduce the therapeutic efficacy of FLUDARABINE EBEWE.

In clinical investigation, pharmacokinetic parameters after peroral administration were not significantly affected by concomitant food intake.

Clinical studies and *in vitro* experiments showed that using fludarabine phosphate in combination with cytarabine may increase intracellular concentration and intracellular exposure of Ara-CTP (active metabolite of cytarabine) in leukaemic cells. Plasma concentrations of Ara-C and the elimination rate of Ara-C were not affected.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Due to the genotoxic risk of fludarabine phosphate females of childbearing potential must be apprised of the potential hazard to the foetus.

Females of child-bearing potential must take effective contraceptive measures during and at least for 6 months after cessation of therapy. Male patients must use effective methods of contraception and be advised to not father a child while receiving fludarabine, and following completion of treatment. Prior to fludarabine treatment, patients must seek advice on fertility preservation options. After fludarabine treatment, patients planning pregnancy are advised to seek genetic counselling.

Studies in mice, rats and dogs have demonstrated dose-related adverse effects on the male reproductive system. Observations consisted of a decrease in mean testicular weights in dogs and degeneration and necrosis of spermatogenic epithelium of the testes in mice, rats and dogs. These results indicate that fludarabine phosphate may adversely affect male fertility, but this has not been directly investigated in studies of reproductive function. No information is available from animal studies on potential effects on female fertility. The possible adverse effects on fertility in humans have not been adequately evaluated.

Use in pregnancy

Category D

Fludarabine is contraindicated in pregnancy (see Section 4.3 Contraindications). FLUDARABINE EBEWE should not be used during pregnancy. One case of fludarabine phosphate use during early pregnancy leading to skeletal and cardiac malformation in the newborn has been reported. Early pregnancy loss has been reported in fludarabine phosphate as well as in combination therapy. Premature delivery has been reported.

Fludarabine phosphate has been shown to be genotoxic. Fludarabine phosphate has been shown to be embryotoxic, fetotoxic and teratogenic in animal studies. Preclinical data in rats demonstrated a transfer of fludarabine phosphate and/or metabolites through the foeto-placental barrier. In view of the small exposure margin between teratogenic doses in animals

and the human therapeutic dose as well as in analogy to other antimetabolites, which are assumed to interfere with the process of differentiation, the therapeutic use of fludarabine phosphate is associated with a relevant risk of teratogenic effects in humans.

Fludarabine phosphate may cause foetal harm when administered to pregnant females. Therefore, fludarabine phosphate must not be used during pregnancy. Females of childbearing potential receiving fludarabine phosphate should be advised to avoid becoming pregnant, and to inform the treating physician immediately should this occur.

Due to the genotoxic risk of fludarabine phosphate, females Sof child-bearing potential or fertile males must take contraceptive measures during and at least for 6 months after cessation of therapy. If the patient becomes pregnant while taking this medicine, the patient should be advised of the potential hazard to the foetus.

Use in lactation

It is not known whether this medicine is 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 in nursing infants from FLUDARABINE EBEWE, breast-feeding should not be initiated during FLUDARABINE EBEWE treatment. Nursing women should discontinue breastfeeding for the duration of FLUDARABINE EBEWE therapy.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

FLUDARABINE EBEWE may reduce the ability to drive or use machines, since fatigue, weakness, visual disturbances, confusion, agitation and seizures have been observed. Patients experiencing such adverse effects should avoid driving and using machines. Reactions can be particularly impaired due to insufficient sleep duration, individual sensitivity and dosage.

4.8. UNDESIRABLE EFFECTS

Based on the experience with the intravenous use of fludarabine phosphate, 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, mucositis, malaise, anorexia, peripheral neuropathy, visual disturbances, stomatitis, skin rashes, and mucositis. Serious opportunistic infections have occurred in CLL patients treated with fludarabine phosphate. Fatalities as a consequence of serious adverse events have been reported.

The table below reports adverse events by MedDRA system organ classes (MedDRA SOCs)

The frequencies are based on clinical trial data regardless of the causal relationship with fludarabine phosphate. The rare adverse reactions were mainly identified from post marketing experience.

System Organ Class MedDRA	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000
Infections and infestations	Infections / opportunistic infections (like latent viral reactivation, e.g. Herpes zoster			Lymphoproliferative disorder (EBV-associated)

System Organ Class MedDRA	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000
	virus, Epstein-Barr-virus, progressive multifocal leucoencephalopathy) Pneumonia			
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)		Skin cancer
Blood and lymphatic system disorders	Neutropenia Anaemia Thrombocytopenia	Myelosuppression		
Immune system disorders			Autoimmune disorder (including autoimmune haemolytic anaemia, thrombocytopenic purpura, acquired haemophilia, pemphigus, Evan's syndrome, acquired haemophilia)	
Metabolism and nutrition disorders		Anorexia	Tumour lysis syndrome (including renal failure, hyperkalemia, metabolic acidosis, haematuria, urate crystalluria, hyperuricaemia, hyperphosphataemia, hypocalcaemia)	
Nervous system disorders		Neuropathy peripheral	Confusion	Agitation, Seizures Coma
Eye disorders		Visual disturbance		Optic neuritis Optic neuropathy Blindness
Cardiac disorders				Heart failure Arrhythmia

System Organ Class MedDRA	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1000 to < 1/100	Rare ≥ 1/10,000 to < 1/1000
Respiratory, thoracic and mediastinal disorders	Cough		Pulmonary toxicity (including dyspnoea, pulmonary fibrosis, pneumonitis)	
Gastrointestinal disorders	Nausea Vomiting Diarrhoea	Stomatitis	Gastrointestinal haemorrhage Pancreatic enzymes abnormal	
Hepatobiliary disorders			Hepatic enzyme abnormal	
Skin and subcutaneous tissue disorders		Rash		Skin cancer, Stevens-Johnson syndrome Necrolysis epidermal toxic (Lyell type)
Renal and urinary disorder				Haemorrhagic cystitis
General disorders and administration site conditions	Fever Fatigue Weakness	Chills Malaise Oedema Mucositis		

Postmarketing Experience

Postmarketing experience with unknown frequency

- Nervous system disorders
    - Leukoencephalopathy (see Section 4.4 Special warnings and precautions for use)
    - Acute toxic leukoencephalopathy (see Section 4.4 Special warnings and precautions for use)
    - -Reversible posterior leukoencephalopathy syndrome (RPLS) (See Section 4.4 Special warnings and precautions for use)
- Vascular disorders
    - Haemorrhage (including cerebral hemorrhage, pulmonary haemorrhage, haemorrhagic cystitis)

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9. OVERDOSE

High doses of fludarabine phosphate have been associated with leukoencephalopathy, acute toxic leukoencephalopathy, 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 FLUDARABINE EBEWE overdosage. Treatment consists of drug discontinuation and supportive therapy.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

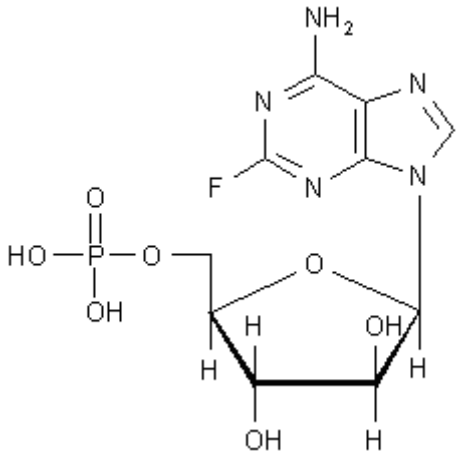
5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, purine analogues

ATC code: L01B B05.

The chemical name of Fludarabine phosphate is 9-β-D-arabinofuranosyl-2-fluoroadenine 5'-(dihydrogen phosphate). Its molecular formula is $C_{10}H_{13}FN_5O_7P$ (Molecular Weight: 365.2) and its chemical structure is:



Mechanism of action

Fludarabine phosphate, a fluorinated nucleotide analogue of the antiviral agent vidarabine, (9-β-D-arabinofuranosyladenine) that is relatively resistant to deamination by adenosine deaminase.

Fludarabine phosphate is rapidly dephosphorylated to fludarabine (2F-ara-A) which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, fludarabine 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 occurs.

Whilst some aspects of the mechanism of action of fludarabine triphosphate 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 chronic lymphocytic leukaemia (CLL) lymphocytes to fludarabine (2F-ara-A) triggers extensive DNA fragmentation and cell death characteristic of

apoptosis. Fludarabine phosphate has also been shown to trigger these changes in normal (non-malignant) lymphoid cells.

Clinical trials

The following information refers to the use of fludarabine phosphate in first line chronic lymphocytic leukaemia.

Intravenous fludarabine 25 mg/m^2 on days 1 - 5 of a 28-day cycle significantly delayed disease progression compared with comparators in the first line treatment of B-cell CLL in three randomised controlled trials (Table 1, Table 2, and Table 3). A difference in survival was not shown due to insufficient follow up and confounding as a result of cross-overs. There was a median 7 and maximum 21 treatment cycles.

Table 1

IV Fludarabine – TRIAL 1 (Spirano) – median duration 8 cycles vs chlorambucil 30 mg/m^2 orally on days 1,15 plus methylprednisolone 40 mg/m^2 intramuscularly on days 1 to 5 and 15 to 19 every 28 days (C/MP)			
	Fludarabine n=75	**C/MP n=75**	**Difference (95% CI)**
Complete response rate %[1]	25	21	4 (-10, 18)
Median time to progression months	26	21	Hazard ratio = 0.53 (0.35,0.79)
Median survival months	> 48	> 48	

[1] US National Cancer Institute Working Group 1988 (NCI) criteria

Table 2

IV Fludarabine - TRIAL 2 (Inveresk) - duration 6 cycles vs cyclophosphamide 750 mg/m^2 IV on day 1 plus doxorubicin 50 mg/m^2 IV on day 1 plus prednisone 40 mg/m^2 orally on days 1-5 every 28 days (CAP).			
	Fludarabine n=53	**C/MP n=52**	**Difference (95% CI)**
Complete response rate %[2]	17	8	9 (6,28)
Median time to progression months	41	17	Hazard ratio = 0.46 (0.30,0.71)
Median survival months	65	53	

[2] International Workshop on CLL criteria 1989 (IWCLL) criteria

Table 3

IV Fludarabine - TRIAL 3 (CALGB) - median duration 7 cycles vs chlorambucil 40 mg/m^2 orally on day 1 every 28 days			
	Fludarabine n=175	**Chlorambucil n=178**	**Difference (95% CI)**
Complete response rate %[3]	15	3	12(4,19)
Median time to progression months	17	13	Hazard ratio = 0.55(0.39,0.76)
Median survival months	56	55	4

[3] Modified US National Cancer Institute Working Group 1988 criteria

Fludarabine tablets were assessed in an uncontrolled trial in 81 patients for first line treatment of B-cell CLL. The dose was 40 mg/m^2 on days 1 - 5 of each 28-day treatment cycle for a mean of 6 cycles. Fewer patients in this trial had Rai stage III/IV disease (22%) than in the intravenous fludarabine trials (35 - 50%). The median time to disease progression had not been

reached at the time of the analysis, but exceeded 38 months, which is comparable or better than the result in the intravenous trials. The NCI complete response rate was 12% and overall response rate 80%. In a subgroup analysis, patients with Rai stage III or IV disease had a response rate of 61%, which is comparable to that observed in this subgroup in the IV studies. There were no data on survival.

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of fludarabine (2F-ara-A) has been studied after intravenous administration by rapid bolus injection, short-term infusion and following continuous infusion as well as after peroral dosing of fludarabine phosphate (2F-ara-AMP).

No clear correlation was found between fludarabine pharmacokinetics and treatment efficacy in cancer patients. However, occurrence of neutropenia and haematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses haematopoiesis in a dose dependent manner.

Absorption

After single dose infusion of 25 mg fludarabine phosphate per m^2 to CLL patients for 30 minutes, fludarabine (2F-ara-A) reached mean maximum concentrations in the plasma of 3.5 - 3.7 μM at the end of the infusion.

Corresponding fludarabine (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, fludarabine (2F-ara-A) plasma trough levels increased by a factor of about 2. An accumulation of fludarabine (2F-ara-A) over several treatment cycles can be excluded. Post-maximum 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.

After peroral fludarabine phosphate (2F-ara-AMP) doses, maximum fludarabine (2F-ara-A) plasma levels reached approximately 20 - 30% of corresponding IV levels at the end of infusion and occurred 1 - 2 hours post dose. The mean systemic fludarabine (2F-ara-A) availability was in the range of 50 - 65% following single and repeated doses and was similar after ingestion of a solution or immediate release tablet formulation. After peroral dosing of fludarabine phosphate (2F-ara-AMP) with concomitant food intake, a slight increase (< 10%) of systemic availability (AUC), a slight decrease of maximum plasma levels (C_{max}) of fludarabine (2F-ara-A) and a delayed time of occurrence of C_{max} was observed. Terminal half-lives were unaffected.

Distribution

An interstudy comparison of fludarabine (2F-ara-A) pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 mL/min/m^2 (2.2 mL/min/kg) and a mean volume of distribution (V_{ss}) of 83 L/m^2 (2.4 L/kg). Data showed a high inter-individual variability. After IV and peroral administration of fludarabine phosphate tablets in doses of 50 - 90 mg, the plasma concentration of fludarabine phosphate and the area under the plasma concentration time curve increased linearly with the dose. Additionally, after IV administration half-lives, plasma clearance and volumes of distribution remained constant independent of the dose indicating a dose linear behaviour.

In vitro investigations with human plasma proteins revealed no pronounced tendency of fludarabine (2F-ara-A) protein binding.

Metabolism

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

Excretion

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

Impaired Renal Function

Individuals with impaired renal function exhibited a reduced total body clearance, indicating the need for a dose reduction. Three groups of CLL/non-Hodgkin's lymphoma patients with differing creatinine clearance, > 70 (n = 10), 30 - 70 (n = 9), < 30 (n = 2) mL/min, were compared. After a single dose of 25 mg fludarabine by 30-minute IV infusion, AUC increased 16% in the second group and 116% in the third group relative to the first group. Multiple adjusted IV doses were then given over 5 days. The first group received 25 mg/m^2/day, the second 20 mg/m^2/day and the third 15 mg/m^2/day. AUC was equivalent in the first and second groups, but increased 41% in the third group. [Note - Fludarabine is not recommended for patients in the third group (see Section 4.3 Contraindications).] There was a statistically significant inverse correlation between fludarabine AUC and creatinine clearance.

Cellular Pharmacokinetics of Fludarabine Triphosphate

Fludarabine (2F-ara-A) is actively transported into leukaemic cells, whereupon it is rephosphorylated to the monophosphate and subsequently to the di- and triphosphate. The triphosphate 2F-ara-ATP is the major intracellular metabolite and the only metabolite known to have cytotoxic activity. Maximum 2F-ara-ATP levels in leukaemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited a considerable variation with a median peak concentration of approximately 20 µM. 2F-ara-ATP levels in leukaemic cells were always considerably higher than maximum 2F-ara-A levels in the plasma indicating an accumulation at the target sites. *In-vitro* incubation of leukaemic lymphocytes showed a linear relationship between extracellular 2F-ara-A exposure (product of 2F-ara-A concentration and duration of incubation) and intracellular 2F-ara-ATP enrichment. 2F-ara-ATP elimination from target cells showed median half-life values of 15 and 23 hours.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

Fludarabine phosphate has been shown not to cause gene mutations in bacterial and mammalian cells *in vitro*. Chromosomal aberrations were observed in an *in vitro* assay using Chinese hamster ovary (CHO) cells under metabolically activated conditions. Fludarabine phosphate has also been shown to be clastogenic in the *in vivo* mouse micronucleus test. In addition, fludarabine phosphate was shown to cause increased sister chromatid exchanges using an *in vitro* sister chromatid exchange (SCE) assay under both metabolically activated and non-activated conditions.

Carcinogenicity

No animal carcinogenicity studies with FLUDARABINE EBEWE have been conducted. However, positive findings in carcinogenicity studies with other cytotoxic medicines and the

positive genotoxicity findings with fludarabine phosphate suggest that FLUDARABINE EBEWE has carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Sodium phosphate – dibasic dihydrate, and sodium hydroxide in water for injections to give a solution containing 25 mg/mL of fludarabine phosphate for intravenous administration.

6.2. INCOMPATIBILITIES

The formulation for intravenous use must not be mixed with other medicines.

6.3. SHELF LIFE

3 years from date of manufacture.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at 2 °C – 8 °C (refrigerate, do not freeze).

6.5. NATURE AND CONTENTS OF CONTAINER

Single dose clear glass vials containing 50 mg of fludarabine phosphate in 2 mL. Available in packs of 1 vial, 5 vials and 10 vials.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Instructions for Use/Handling

Each mL of Fludarabine Ebewe injection contains 25 mg of fludarabine phosphate, with sodium phosphate (dibasic dihydrate) and sodium hydroxide in water for injections. The pH range for the product is 7.2 to 7.8.

In clinical studies, the product has been diluted in 100 mL or 125 mL of 5% dextrose injection or 0.9% sodium chloride. The product may also be diluted with 5% glucose injection.

FLUDARABINE EBEWE contains no antimicrobial preservative. To reduce microbiological hazards it is recommended that any dilution should be effected immediately prior to use and infusion commenced as soon as practicable after preparation of infusion solutions. If storage is necessary, store at 2°C - 8°C (refrigerate, do not freeze) for not more than 24 hours after preparation. Administration should be completed within 24 hours of preparation of the infusion and any residue discarded according to the guidelines for the disposal of cytotoxic drugs. Any solutions, which are discoloured, hazy or contain visible particulate matter, should not be used.

FLUDARABINE EBEWE should not be handled by pregnant staff.

Procedures for proper handling and disposal should be observed. Consideration should be given to handling and disposal according to guidelines used for cytotoxic medicines. Any spillage or waste material may be disposed of by incineration.

Caution should be exercised in the handling and preparation of the FLUDARABINE EBEWE 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.

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

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

21/09/2016

10. DATE OF REVISION OF THE TEXT

03/12/2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.6	Revision to fertility, contraception, pregnancy and breastfeeding information
4.8	Update to adverse reporting URL
4.9	Additional symptoms of overdose included
8	Change in sponsor details