NEW ZEALAND DATA SHEET

1 FLUDARA® 50 MG/2 ML, POWDER FOR INJECTION AND FLUDARA® ORAL 10 MG FILM COATED TABLET

FLUDARA 50 mg/2 mL powder for injection.*

FLUDARA ORAL 10 mg film coated tablet.

* Not marketed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fludarabine phosphate.

FLUDARA vial of sterile lyophilised solid cake contains 50mg of the active ingredient fludarabine phosphate. Reconstitution with 2mL of Sterile Water for Injection results in a solution containing 25mg/mL of fludarabine phosphate for intravenous administration.

FLUDARA oral film coated tablets contain 10 mg of fludarabine phosphate.

For the full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Powder for injection and film coated tablet.

FLUDARA vial contains a sterile lyophilised solid cake for reconstitution.

FLUDARA oral film coated tablets are salmon coloured oval shaped tablets with "LN" indented in a regular hexagon on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dose

Formulation for intravenous use

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

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

Adults

The recommended dose is 25mg/m^2 body surface given daily for 5 consecutive days every 28 days by the intravenous route. Each vial is to be made up in 2mL water for injection. Each mL of the resulting solution will contain 25mg fludarabine phosphate.

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 10mL of physiological saline. Alternatively, the required dose drawn up in a syringe may be diluted into 100mL physiological saline and infused over approximately 30 minutes.

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

Tablets for oral use

Adults

FLUDARA tablets should be prescribed by a qualified physician experienced in the use of antineoplastic therapy.

The recommended dose is 40 mg fludarabine phosphate/m^2 body surface given daily for 5 consecutive days every 28 days by the oral route. FLUDARA tablets can be taken either on an empty stomach or together with food. The tablets are to be swallowed whole with water, and must not be chewed or broken.

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

Toxicity

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

Impaired State of Health

A number of clinical settings may predispose to increased toxicity from FLUDARA. These include advanced age, renal insufficiency and bone marrow impairment- see Section 4.4, Use in Specialised groups, Impaired state of health. Such patients should be monitored closely for excessive toxicity and the dose modified accordingly.

Impaired renal function

Dosage reduction is required in renally impaired patients. Refer to "Section 5.2 - Impaired Renal Function" and "Section 4.4 - Use in renal impairment" sections of this document.

Retreatment options after initial FLUDARA treatment

Patients who primarily respond to FLUDARA have a good chance of responding again to FLUDARA monotherapy. A crossover from initial treatment with FLUDARA to chlorambucil for non responders to FLUDARA 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.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Renal impairment with creatinine clearance < 30 mL / min
- Hemolytic anemia

FLUDARA 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, FLUDARA was associated with severe neurologic effects, including blindness, coma and death. Symptoms appeared from 21 to 60 days from last dose. This severe central nervous system toxicity occurred in 36% of patients treated intravenously with doses approximately four times greater (96mg/m2/day for 5 - 7 days) than the dose recommended for treatment of CLL.

Similar severe central nervous system toxicity has also been observed in patients treated at doses recommended for CLL. Confusion occurred uncommonly and coma, seizures and agitation rarely (see Section 4.8).

In postmarketing experience, neurotoxicity has also been reported to occur with a latency ranging from 7 to 225 days after the last dose of FLUDARA.

The effect of chronic administration of FLUDARA on the central nervous system is unknown. However, patients tolerated the recommended dose, in some studies for relatively

long treatment times (for up to 26 courses of therapy). Patients should be closely observed for signs of neurologic side effects.

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

These may occur:

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

FLUDARA 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.

Disease progression

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

Tumour lysis syndrome

Tumour lysis syndrome associated with FLUDARA treatment has been reported in CLL patients with large tumour burdens. Since FLUDARA can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this complication.

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 FLUDARA. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with FLUDARA.

Patients undergoing treatment with FLUDARA should be closely monitored for signs of haemolysis. Discontinuation of therapy with FLUDARA 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 drugs. 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.

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 FLUDARA in patients

with renal impairment and 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 70mL / min). FLUDARA must be administered cautiously in patients with renal insufficiency. In patients with moderate impairment of renal function (creatinine clearance between 30 and 70mL / min), the dose should be reduced in proportion to the reduced creatinine clearance and close haematological monitoring should be used to assess toxicity. FLUDARA treatment is contraindicated, if creatinine clearance is < 30mL / min.

Use in hepatic impairment

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

Paediatric Use

FLUDARA is not recommended for the use in children below age 18 due to a lack of data on safety and efficacy.

Use in the Elderly

Since there are limited data for the use of FLUDARA in elderly persons (> 75 years), caution should be exercised with the administration of FLUDARA in these patients.

Vaccination

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

In a clinical investigation using FLUDARA in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukaemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of FLUDARA in combination with pentostatin is not recommended.

A pharmacokinetic drug 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 FLUDARA treatment.

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Category D

FLUDARA should not be used during pregnancy. There are very limited data of FLUDARA use in pregnant women in the first trimester. 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 FLUDARA monotherapy as well as in combination therapy. Premature delivery has been reported.

FLUDARA has been shown to be embryotoxic and/or teratogenic in animal studies. Preclinical data in rats demonstrated a transfer of fludarabine phosphate and /or metabolites through the feto-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 FLUDARA is associated with a relevant risk of teratogenic effects in humans.

Women should avoid becoming pregnant while on FLUDARA therapy

Females of 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 drug, the patient should be advised of the potential hazard to the foetus.

Breastfeeding

It is not known whether this drug 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 FLUDARA, breast feeding should be discontinued for the duration of FLUDARA therapy.

Breastfeeding should not be initiated during FLUDARA treatment.

Fertility

Studies in mice, rats and dogs indicate that fludarabine phosphate may adversely affect male fertility, but this has not been directly investigated in studies of reproductive function (see Section 5.3). 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

FLUDARA 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

4.8 UNDESIRABLE EFFECTS

Based on the experience with the intravenous use of FLUDARA, the most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anaemia), infection including pneumonia, cough, fever, fatigue, weakness, nausea, vomiting and diarrhoea.

Other commonly reported events include chills, oedema, malaise, anorexia, peripheral neuropathy, visual disturbances, stomatitis, skin rashes, and mucositis. Serious opportunistic infections have occurred in CLL patients treated with FLUDARA. 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 FLUDARA. The rare adverse reactions were mainly identified from post marketing experience.

Table 1 - Adverse events reported in clinical trials or during post-marketing surveillance in patients treated with Fludara

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 virus Epstein-Barr-virus Progressive multifocal leucoencephalopathy), Pneumonia			Lympho-proliferative 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
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, Anemia, Thrombocytopenia	Myelosuppression		
Immune system disorders			Autoimmune disorder (including Autoimmune haemolytic anaemia, Thrombocytopenic purpura, Pemphigus, Evans syndrome, Acquired haemophilia)	
Metabolism and nutrition disorders		Anorexia	Tumor 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
Vascular disorders			Gastrointestinal haemorrhage	
Respiratory, thoracic and mediastinal disorders	Cough		Pulmonary toxicity (including Dyspnoea, Pulmonary fibrosis, Pneumonitis)	
Gastrointestinal disorders	Nausea, Vomiting, Diarrhoea	Stomatitis	Pancreatic enzymes abnormal	
Hepatobiliary disorders			Hepatic enzyme abnormal	
Skin and subcutaneous tissue disorders		Rash		Skin cancer, Stevens-Johnson syndrome, Necrolysis epidermal toxic (Lyell type)
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)
  - Acute toxic leukoencephalopathy (see Section 4.4)
  - Reversible posterior leukoencephalopathy syndrome (RPLS) (see Section 4.4)
- 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://nzphvc.otago.ac.nz/report/

4.9 OVERDOSE

High doses of FLUDARA 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 FLUDARA overdosage. Treatment consists of drug discontinuation and supportive therapy.

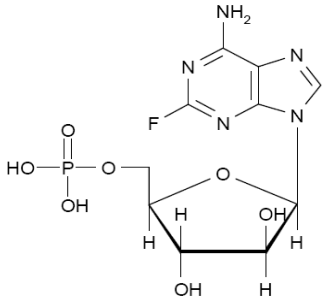
In cases of overdose, it is advisable to contact the New Zealand National Poisons Information Centre (telephone 0800 POISON or 0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Chemical structure



Molecular Formula: $C_{10}H_{13}FN_5O_7P$

Molecular Weight: 365.2

Chemical Name: 9-β-D-arabinofuranosyl-2-fluoroadenine 5'-(dihydrogen phosphate).

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

Mechanism of action

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 efficacy and safety

The following information refers to the use of FLUDARA in 1st line chronic lymphocytic leukaemia.

Intravenous fludarabine 25mg/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 (Tables 2-4). 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 2 - IV FLUDARABINE – TRIAL 1 (Spirano) – median duration 8 cycles vs chlorambucil 30mg/m2 orally on days 1, 15 plus methylprednisolone 40mg/m2 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 mths	26 21	Hazard ratio = 0.53 (0.35,0.79)
Median survival mths	>48	>48

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

Table 3 - V FLUDARABINE – TRIAL 2 (Inveresk) – duration 6 cycles vs cyclophosphamide 750mg/m2 IV on day 1 plus doxorubicin 50mg/m2 IV on day 1 plus prednisone 40mg/m2 orally on days 1 - 5 every 28 days (CAP)

Fludarabine n=53	CAP n=52	Difference (95% CI)
Complete response rate[1] %	17 8	9 (6,28)
Median time to progression mths	41 17	Hazard ratio = 0.46 (0.30,0.71)
Median survival mths	65	53

[1] International Workshop on CLL criteria 1989 (IWCLL) criteria.

Table 4 - IV FLUDARABINE – TRIAL 3 (CALGB) – median duration 7 cycles vs chlorambucil 40mg/m2 orally on day 1 every 28 days

Fludarabine n=175	Chlorambucil n=178		Difference (95% CI)
Complete response rate[1] %	15	3	12 (4,19)
Median time to progression mths	17	13	Hazard ratio = 0.55 (0.39,0.76)
Median survival mths	56	55	4

[1] 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 40mg/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

Absorption

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.

Distribution

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.

After single dose infusion of 25 mg fludarabine phosphate per m2 to CLL patients for 30 minutes, fludarabine (2F-ara-A) reached mean maximum concentrations in the plasma of 3.5-3.7µM 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.

Biotransformation

An interstudy comparison of fludarabine (2F-ara-A) pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 mL/min/m2 (2.2 mL/min/kg) and a mean volume of distribution (V_{ss}) of 83 L/m2 (2.4 L/kg). Data showed a high interindividual variability. After i.v. and peroral administration of fludarabine phosphate tablets in doses of 50–90mg, the plasma concentration of fludarabine phosphate and the area under the plasma concentration time curve increased linearly with the dose. Additionally, after i.v administration half lives, plasma clearance and volumes of distribution remained constant independent of the dose indicating a dose linear behaviour.

After peroral fludarabine phosphate (2F-ara-AMP) doses, maximum fludarabine (2F-ara-A) plasma levels reached approximately 20-30% of corresponding i.v. 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 Cmax was observed. Terminal half lives were unaffected. In vitro investigations with human plasma proteins revealed no pronounced tendency of fludarabine (2F-ara-A) protein binding.

Excretion

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

Special Populations

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 leukemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited a considerable variation with a median peak concentration of approximately 20µM. 2F-ara-ATP levels in leukemic cells were always considerably higher than maximum 2F-ara-A levels in the plasma indicating an accumulation at the target sites. In-vitro incubation of leukemic lymphocytes showed a linear relationship between extracellular 2F-ara-A exposure (product of 2F-ara-A concentration and duration of incubation) and intracellular 2F-ara-ATP enrichment. 2F-ara-ATP elimination from target cells showed median half life values of 15 and 23 hours.

Renal Impairment

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 25mg 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 25mg/m2/day, the second 20mg/m2/day and the third 15mg/m2/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).] There was a statistically significant inverse correlation between fludarabine AUC and creatinine clearance.

5.3 PRECLINICAL SAFETY DATA

Carcinogenicity

No animal carcinogenicity studies with FLUDARA have been conducted. However, positive findings in carcinogenicity studies with other cytotoxic drugs and the positive genotoxicity findings with fludarabine phosphate suggest that FLUDARA has carcinogenic potential. 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.

Fertility

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

FLUDARA I.V.

Mannitol

Sodium hydroxide

FLUDARA ORAL

Microcrystalline cellulose

Lactose

Colloidal silicon dioxide

Croscarmellose sodium

Magnesium stearate

Hypromellose

Purified talc

Titanium dioxide

Iron oxide red

Iron oxide yellow

6.2 INCOMPATIBILITIES

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

Not applicable for the tablets.

6.3 SHELF LIFE

FLUDARA I.V.

36 months.

Reconstituted FLUDARA contains no antimicrobial preservative. To reduce microbiological hazards it is recommended that reconstitution and / or further dilution should be effected immediately prior to use and infusion commenced as soon as practicable after reconstitution. After reconstitution if storage is necessary, store in a refrigerator at 4°C for not more than 24 hours or 8 hours at room temperature. Any solutions which are discoloured, hazy or contain visible particulate matter should not be used. Do not freeze.

FLUDARA ORAL

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

FLUDARA I.V.

Unopened: Store at or below 30°C.

Reconstituted: Store at 4°C, refrigerate, do not freeze (see Section 6.4)

FLUDARA ORAL

Store at or below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

*FLUDARA I.V.**

10mL capacity clear glass vials containing 50mg of fludarabine phosphate as a lyophilised cake. Packaged in single dose vial cartons in boxes of 5.

FLUDARA ORAL

The film coated tablets are supplied in blisters of 5 tablets each. Packs of three or four blisters are available and are packed in child resistant containers.

*Not marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Instructions For Use / Handling of the intravenous dose form

FLUDARA should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2mL of sterile water for injection, the solid cake should fully dissolve in 15 seconds or less. Each mL of the resulting solution will contain 25mg of fludarabine phosphate, 25mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. The pH range for the final product is 7.2 and 8.2. In clinical studies the product has been diluted in 100mL or 125mL of 5% dextrose injection or 0.9% sodium chloride.

FLUDARA 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 drugs. Any spillage or waste material may be disposed of by incineration.

Caution should be exercised in the handling and preparation of the FLUDARA solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution comes into contact with the skin or mucous membranes, the area should be washed thoroughly with soap and water. In the event of contact with the eyes, rinse them thoroughly with copious amounts of water. Exposure by inhalation should be avoided.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

Australia

Genzyme Australasia Pty Ltd.
Level 1, Building C
12-24 Talavera Road
North Ryde, NSW 2113 Australia
Toll Free Number (medical information): 1800 818 806
Email: medinfo.australia@sanofi.com

New Zealand

sanofi-aventis new zealand limited
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56 Cawley Street, Ellerslie,
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Toll Free Number (medical information): 0800 283 684 (option 2)
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9 DATE OF FIRST APPROVAL

11 March 1993

10 DATE OF REVISION

05 February 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Minor editorial changes and movement of text (reformat) to align the New Zealand Data Sheet Template Explanatory Guide