Public Assessment Report

Mutual Recognition Procedure

Fludara Two 50 mg Powder for Solution for Injection for Infusion

UK/H/0817/01
UK Licence no: PL 00053/0347

Schering Healthcare Limited

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Module 1

Product Name	Fludara Two 50 mg Powder for Solution for Injection for Infusion
Type of Application	Article 10c
Active Substance	Fludarabine Phosphate
Form	Powder for Solution for Injection or Infusion
Strength	50mg per vial
MA Holder	Schering Healthcare Limited The Brow, Burgess Hill West Sussex, RH15 9NE United Kingdom
RMS	United Kingdom
CMS	Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Sweden, Italy, Luxembourg, The Netherlands and Portugal.
Procedure Number	UK/H/0817/01
Timetable	D90 – 26th April 2006

Module 2

Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Fludara Two 50 mg powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg Fludarabine phosphate.
1 ml of reconstituted solution contains 25 mg fludarabine phosphate.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

White lyophilisate for reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves.

First line treatment with Fludara Two should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stages A/B) where the patient has disease related symptoms or evidence of progressive disease.

4.2 Posology and method of administration

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

It is strongly recommended that Fludara Two should be only administered intravenously. No cases have been reported in which paravenously administered Fludara Two led to severe local adverse reactions. However, the unintentional paravenous administration must be avoided. Adults The recommended dose is 25 mg fludarabine phosphate/m² body surface given daily for 5 consecutive days every 28 days by the intravenous route. Each vial is to be made up in 2 ml water for injection. Each ml of the resulting solution will contain 25 mg fludarabine phosphate. The required dose (calculated on the basis of the patient's body surface) of the reconstituted solution is drawn up into a syringe. For intravenous bolus injection this dose is further diluted in 10 ml of 0.9 % sodium chloride. Alternatively, for infusion, the required dose may be diluted in 100 ml 0.9 % sodium chloride and infused over approximately 30 minutes (see also section 6.6).

The optimal duration of treatment has not been clearly established. The duration of treatment depends on the treatment success and the tolerability of the drug.

It is recommended that Fludara Two be administered up to the achievement of response (usually 6 cycles) and then the drug should be discontinued.

• Hepatic impairment

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

• Renal impairment

The total body clearance of the principle plasma metabolite 2-F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. Patients with reduced kidney 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). Therefore, if 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 70 ml/min, the dose should be reduced by up to 50% and close haematological monitoring should be used to assess toxicity. Fludara Two treatment is contraindicated, if creatinine clearance is < 30 ml/min.

• Children

The safety and effectiveness of Fludara Two in children has not been established.

4.3 Contraindications

Fludara Two is contraindicated
- in those patients who are hypersensitive to the active substance or any of the excipients,
- in renally impaired patients with creatinine clearance < 30 ml/min,
- in patients with decompensated haemolytic anaemia,
- during pregnancy and lactation.

4.4 Special warnings and precautions for use

When used at high doses in dose-ranging studies in patients with acute leukaemia, Fludara Two was associated with severe neurologic effects, including blindness, coma and death. This severe central nervous system toxicity occurred in 36 % of patients treated with doses approximately four times greater (96 mg/m²/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). Patients should be closely observed for signs of neurologic side effects.

The effect of chronic administration of Fludara Two on the central nervous system is unknown. However, patients tolerated the recommended dose, in some studies for relatively long term treatment times, whereby up to 26 courses of therapy were administered.

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

Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with Fludara Two. 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 haematologic monitoring.

Fludara Two 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.

As with other cytotoxics, caution should be exercised with fludarabine phosphate, when further haematopoietic stem sampling is considered.

Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes to the host) has been observed after transfusion of non-irradiated blood in Fludara Two-treated patients. Fatal outcome as a consequence of this disease has been reported with a high frequency. Therefore, patients who require blood transfusion and who are undergoing, or who have received, treatment with Fludara Two 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 Fludara Two therapy.

Tumour lysis syndrome associated with Fludara Two treatment has been reported in CLL patients with large tumour burdens. Since Fludara Two can indce a response as early as 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 Fludara Two. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with Fludara Two. Patients treated with Fludara Two should be closely monitored for haemolysis.

Patients undergoing treatment with Fludara Two should be closely monitored for signs of autoimmune haemolytic anaemia (decline in haemoglobin linked with haemolysis and positive Coombs test). Discontinuation of therapy with Fludara Two is recommended in case of haemolysis. Blood transfusion (irradiated, see above) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.

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

No data are available concerning the use of Fludara Two in children. Therefore, treatment with Fludara Two in children is not recommended.

Females of child-bearing potential or males must take contraceptive measures during and at least for 6 months after cessation of therapy.

During and after treatment with Fludara Two vaccination with live vaccines should be avoided. A crossover from initial treatment with Fludara Two to chlorambucil for non responders to Fludara Two should be avoided because most patients who have been resistant to Fludara Two have shown resistance to chlorambucil.

4.5 Interaction with other medicinal products and other forms of interaction

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

The therapeutic efficacy of Fludara Two may be reduced by dipyridamole and other inhibitors of adenosine uptake.

A pharmacokinetic drug interaction was observed in CLL and 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 leukaemic cells in terms of intracellular peak concentrations as well as of intracellular exposure (AUC) in combination of Fludara Two and subsequent Ara-C treatment. Plasma concentrations of Ara-C and the elimination rate of Ara-CTP were not affected.

4.6 Pregnancy and lactation

• Pregnancy

Fludara Two should not be used during pregnancy.

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

Very limited human experience supports 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 metabolites through the foeto-placental barrier.

• Lactation

Breast-feeding should be discontinued for the duration of Fludara Two therapy. 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.

4.7 Effects on ability to drive and use machines

The effect of treatment with Fludara Two on the patient's ability to drive or operate machinery has not been evaluated.

4.8 Undesirable effects

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

The most frequently reported adverse events and those reactions which are more clearly related to the drug are arranged below according to body system regardless of their seriousness. Their frequencies (common $\geq$ 1%, uncommon $\geq$ 0.1% and < 1%) are based on clinical trial data regardless of the causal relationship with Fludara Two. The rare events (< 0.1%) were mainly identified from the post-marketing experience.

• Body as a whole

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

• Haemic and lymphatic system

Haematologic events (neutropenia, thrombocytopenia, and anaemia) have been reported in the majority of patients treated with Fludara Two. Myelosuppression may be severe and cumulative. Fludara Two´s prolonged effect on the decrease in the number of T-lymphocytes may lead to increased risk of opportunistic infections, including those due to latent viral reactivation, e.g. Herpes zoster, Epstein-Barr Virus (EBV) or progressive multifocal leucoencephalopathy (see 4.4. “Special warning and precautions for use”). Evolution 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 Fludara Two. The majority of these patients also received prior, concomitant or subsequent treatment with alkylating agents or irradiation. Monotherapy with Fludara Two has not been associated with an increased risk for the development of MDS.

Clinically significant autoimmune phenomena have been reported to occur uncommonly in patients receiving Fludara Two (see section 4.4).

• Metabolic and nutritional disorders

Tumour lysis syndrome has been reported uncommonly in patients treated with Fludara Two. This complication may include hyperuricaemia, hyperphosphataemia, hypocalcaemia, metabolic acidosis, hyperkalaemia, haematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and haematuria. Oedema has been commonly reported. Changes in hepatic and pancreatic enzyme levels are uncommon .

• Nervous system

Peripheral neuropathy has been commonly observed. Confusion is uncommon. Coma, agitation and seizures occur rarely.

• Special senses

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

• Respiratory system

Pneumonia commonly occurs in association with Fludara Two treatment. Pulmonary hypersensitivity reactions to Fludara Two (pulmonary infiltrates/pneumonitis/fibrosis) associated with dyspnoea and cough have been uncommonly observed.

• Digestive system

Gastrointestinal disturbances such as nausea and vomiting, diarrhoea, stomatitis, and anorexia are common events. Gastrointestinal bleeding, mainly related to thrombocytopenia has been uncommonly reported in patients treated with Fludara Two.

• Cardiovascular system

In rare cases, heart failure and arrhythmia have been reported in patients treated with Fludara Two.

• Urogenital system

Rare cases of haemorrhagic cystitis have been reported in patients treated with Fludara Two.

• Skin and appendages

Skin rashes have been commonly reported in patients treated with Fludara Two.

In rare cases a Stevens-Johnson syndrome or a toxic epidermal necrolysis (Lyell's syndrome) may develop.

4.9 Overdose

High doses of Fludara Two have been associated with an 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 Two overdosage. Treatment consists of drug discontinuation and supportive therapy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents
ATC-code L01B B05

Fludara Two contains fludarabine phosphate, a water-soluble fluorinated nucleotide analogue of the antiviral agent vidarabine, 9-ß-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase.

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

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

A phase III trial in patients with previously untreated B-chronic lymphocytic leukaemia comparing treatment with Fludara vs. chlorambucil (40mg / m² q4 weeks) in 195 and 199 patients respectively showed the following outcome: statistically significant higher overall response rates and complete response rates after 1st line treatment with Fludara Two compared to chlorambucil (61.1% vs. 37.6% and 14.9% vs. 3.4%, respectively); statistically significant longer duration of response (19 vs. 12.2 months) and time to progression (17 vs. 13.2 months) for the patients in the Fludara Two group. The median survival of the two patient groups was 56.1 months for Fludara Two and 55.1 months for chlorambucil, a non-significant difference was also shown with performance status. The proportion of patients reported to have toxicities were comparable between Fludara Two patients (89.7%) and chlorambucil patients (89.9%). While the difference in the overall incidence of haematological toxicities was not significant between the two treatment groups, significantly greater proportions of Fludara Two patients experienced white blood cell ($p=0.0054$) and lymphocyte ($p=0.0240$) toxicities than chlorambucil patients. The proportions of patients who experienced nausea, vomiting, and diarrhoea were significantly lower for Fludara Two patients ($p<0.0001$, $p<0.0001$, and $p=0.0489$, respectively) than chlorambucil patients. Toxicities of the liver were also reported for significantly ($p=0.0487$) less proportions of patients in the Fludara Two group than in the chlorambucil group.

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

A randomised trial of Fludara Two vs. cyclophosphamide, adriamycin and prednisone (CAP) in 208 patients with CLL Binet stage B or C revealed the following results in the subgroup of 103 previously treated patients: the overall response rate and the complete response rate were higher with Fludara Two compared to CAP (45% vs. 26% and 13% vs. 6%, respectively); response duration and overall survival were similar with Fludara Two and CAP. Within the stipulated treatment period of 6 months the number of deaths was 9 (Fludara Two) vs. 4 (CAP).

Post-hoc analyses using only data of up to 6 months after start of treatment revealed a difference between survival curves of Fludara Two and CAP in favour of CAP in the subgroup of pretreated Binet stage C patients.

5.2 Pharmacokinetic properties

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

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

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 single dose infusion of 25 mg 2F-ara-AMP per m² to cancer patients for 30 minutes 2F-ara-A reached mean maximum concentrations in the plasma of 3.5 - 3.7 µM at the end of the infusion. Corresponding 2F-ara-A levels after the fifth dose showed a moderate accumulation with mean maximum levels of 4.4 - 4.8 µM at the end of infusion. During a 5-day treatment schedule 2F-ara-A plasma trough levels increased by a factor of about 2. An accumulation of 2F-ara-A over several treatment cycles can be excluded. Postmaximum levels decayed in three disposition phases with an initial half-life of approx. 5 minutes, an intermediate half-life of 1 - 2 hours and a terminal half-life of approx. 20 hours.

An interstudy comparison of 2F-ara-A pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 ± 40 ml/min/m² (2.2 ± 1.2 ml/min/kg) and a mean volume of distribution (Vss) of 83 ± 55 l/m² (2.4 ± 1.6 l/kg). Data showed a high interindividual variability. Plasma levels of 2F-ara-A and areas under the plasma level time curves increased linearly with the dose, whereas half-lives, plasma clearance and volumes of distribution remained constant independent of the dose indicating a dose linear behaviour. Occurrence of neutropenia and haematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses the haematopoiesis in a dose dependent manner.

2F-ara-A elimination is largely by renal excretion. 40 to 60 % of the administered i.v. dose was excreted in the urine. Mass balance studies in laboratory animals with ^{3}H-2F-ara-AMP showed a complete recovery of radio-labelled substances in the urine. Another metabolite, 2F-ara-hypoxanthine, which represents the major metabolite in the dog, was observed in humans only to a minor extent. Individuals with impaired renal function exhibit a reduced total body clearance, indicating the need for a dose reduction. In vitro investigations with human plasma proteins revealed no pronounced tendency of 2F-ara-A protein binding.

• Cellular pharmacokinetics of fludarabine triphosphate

2F-ara-A is actively transported into 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 approx. 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.

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

5.3 Preclinical safety data

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

Systemic toxicity studies following repeated administration of fludarabine phosphate showed also the expected effects on rapidly proliferating tissues above a threshold dose. The severity of morphological manifestations increased with dose levels and duration of dosing and the observed changes were generally considered to be reversible. In principle, the available experience from the therapeutic use of Fludara Two points to 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 indicated a teratogenic potential of fludarabine phosphate. In view of the small safety margin between the teratogenic doses in animals and the human therapeutic dose as well as in analogy to other antimetabolites which are assumed to interfere with the process of differentiation, the therapeutic use of Fludara Two is associated with a relevant 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 known activity of fludarabine phosphate at the DNA-level and the mutagenicity test results form the basis for the suspicion of a tumorigenic potential. No animal studies which directly address the question of tumorigenicity have been conducted, because the suspicion of an increased risk of second tumours due to Fludara Two therapy can exclusively be verified by epidemiological data.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol,
Sodium hydroxide (to adjust the pH to 7.7).

6.2 Incompatibilities

Must not be mixed with other drugs.

6.3 Shelf life

As packaged for sale: 3 years.

Chemical and physical in-use stability after reconstitution has been demonstrated for 7 days at 4 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 to 8 °C or 8 hours at room temperature.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage after reconstitution or dilution, see section 6.3

6.5 Nature and contents of container

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

Each package contains 5 vials.

6.6 Special precautions for disposal

• Reconstitution

Fludara Two should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2 ml of sterile water for injection, the powder should fully dissolve in 15 seconds or less. Each ml of the resulting solution will contain 25 mg of fludarabine phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. The pH range for the final product is 7.2 - 8.2.

• Dilution

The required dose (calculated on the basis of the patient's body surface) is drawn up into a syringe. For intravenous bolus injection this dose is further diluted in 10 ml of 0.9 % sodium chloride. Alternatively, for infusion, the required dose may be diluted in 100 ml of 0.9 % sodium chloride and infused over approximately 30 minutes. In clinical studies, the product has been diluted in 100 ml or 125 ml of 5 % dextrose injection or 0.9 % sodium chloride.

• Inspection prior to use

The reconstituted solution is clear and colourless. It should be visually inspected before use.
Only clear and colourless solutions without particles should be used. Fludara should not be used in case of a defective container.

• Handling and disposal

Fludara Two should not be handled by pregnant staff.

Procedures for proper handling should be followed according to local requirements for cytotoxic drugs.

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

The medicinal product is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of last renewal: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

Module 3

Product Information Leaflet

Fludara Two 50 mg powder for solution for injection or infusion
Fludarabine phosphate

Read all of this leaflet carefully before this medicine is given to you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT FLUDARA TWO IS AND WHAT IT IS USED FOR

What is Fludara Two?

Fludara Two is an anti-cancer drug for intravenous injection or infusion.

How does Fludara Two work?

All cells of the body produce new cells like themselves by dividing. For this purpose, the cells´ genetic material (DNA) must be copied and reproduced. Fludara Two works by hindering the production of new DNA. Therefore, when Fludara Two is taken up by the cancer cells, it stops the growth of new cancer cells.

In cancers of the white blood cells (as chronic lymphocytic leukaemia) many abnormal lymphocytes are produced and lymph nodes start to grow in various regions of your body. The abnormal lymphocytes either do not work properly or are too young (immature) to carry out the normal disease fighting functions of white blood cells. If there are too many of these abnormal lymphocytes, they push aside healthy blood cells in the bone marrow where most of the new blood cells are formed. Without enough healthy blood cells, infections, anaemia (decrease in number of red blood cells), bruising, unusual strong bleeding or even organ failure can result.

What Fludara Two is used for:

Fludara is used in the treatment of B-cell chronic lymphocytic leukaemia (B-CLL) in patients with sufficient healthy blood cell production. This is a cancer of the white blood cells (called *lymphocytes*).

First treatment for chronic lymphocytic leukaemia with Fludara Two should only be started in patients with advanced disease having disease-related symptoms or evidence of disease progression.

2. BEFORE YOU ARE GIVEN FLUDARA TWO

Do not use Fludara Two:

- if you are **allergic** (*hypersensitive*) to fludarabine phosphate or any of the other ingredients of Fludara Two.
- if you are **pregnant or breast-feeding.**
- if **your kidney function is severely reduced.**
- if **you have lower numbers of red blood cells because of a certain type of anaemia** *(decompensated haemolytic anaemia)*. Your doctor will have told you if you have this condition.

If any of the above applies to you or if you are not sure, **tell your doctor.**

Take special care with Fludara Two:

- If your bone marrow is not working properly or if you have a poorly functioning or depressed immune system or a history of serious infections, your doctor may decide to not give you this medicine, or may take preventative measures.
  - **If - before treatment is started - you are feeling extremely unwell, if you notice any unusual bruising, more bleeding than usual after injury, or if you are catching a lot of infections,** tell your doctor.

- If you notice any unusual symptoms of your nervous system, tell your doctor. This is because **blindness, coma and death** have been reported in patients on doses four times greater than recommended.

- You will have regular blood tests during treatment and you will be closely monitored.
The disease itself and the therapy may cause a reduction of the number of blood cells, and your immune system may attack different parts of your body **(called 'autoimmune phenomenon'**). It may also be directed against your red blood cells **(called 'autoimmune haemolysis')**. This condition can be life-threatening and even lead to death.
If this condition occurs you may receive further medication such as transfusion of irradiated blood (see below) and adrenocorticoids.

- **If you notice any unusual bruising, more bleeding than usual after injury or if you seem to be catching a lot of infections, if you have a red to brownish urine, or have a rash or any blisters on your skin,** tell your doctor immediately.

- If you need to have stem cells collected and you are being (or have been) treated with Fludara Two, tell your doctor.

- If you need a blood transfusion and you are being (or have been) treated with Fludara Two, tell your doctor. Your doctor will ensure that you receive blood only, which has gone through a special treatment called irradiation. There have been severe complications and even death, when nonirradiated blood has been given.

- If you have or have had skin cancer it may worsen or flare up again during or after Fludara Two therapy.
- **If you notice any changes to your skin either while you are receiving this medicine or after you have finished the therapy,** tell your doctor.

- If your disease is very severe, your body may not be able to clear all the waste products from the cells destroyed by Fludara Two. This **may cause kidney failure and heart problems** and can happen from the first week of treatment**.** Your doctor will be aware of this and may give you other medicines to help prevent this.
- **• If you notice any pain in your side, blood in your urine or reduced amount of urine,** tell your doctor immediately.
-

What you should also consider, when you are treated with Fludara Two:

- Contraception: If you are fertile, **use contraception during treatment and for at least 6 months afterwards**: Both women and men, who may still be fertile should **use a reliable form of contraception**. This is because it cannot be ruled out that Fludara Two may harm an unborn baby.

- Double check on vaccinations: **Check with your doctor** on any vaccinations you may need, because
live vaccinations should be avoided during and after treatment with Fludara Two.

- Kidney function: **If you have kidney problems or are over the age of 70 years**, you will have regular blood and/or laboratory tests to check your kidney function, see also section 'Do not use Fludara Two' and section 3. How to use Fludara Two.

- Liver function: **If your liver does not work properly**, your doctor may give you this medicine with caution.

Taking or using other medicines:

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not receive Fludara Two in combination with another drug called pentostatin (deoxycoformycin), which is also used to treat chronic lymphocytic leukaemia as this may lead to severe lung complications.

The effectiveness of Fludara Two may be reduced by dipyridamole (a medication which may be prescribed to prevent excessive blood clotting) or other substances, which work similarly.

• Ask your doctor or pharmacist for advice before taking any medicine.

Elderly patients:
If you are over 75 years old, you will be monitored very closely because only limited data are available for this population. **If you are over the age of 70 years,** you will have regular blood and/or laboratory tests to control your kidney function, see also section 3. How to use Fludara Two.

Children:
The safety and efficacy of Fludara Two has not been established in children.

Pregnancy:
- **If you are pregnant or you think you may be pregnant**, tell your doctor immediately.
- **If you are a woman who may still be fertile** avoid becoming pregnant by using effective contraceptive methods during treatment and for at least 6 months after treatment.
- **Men who have been given Fludara Two** and who could become fathers must use reliable contraception during and for at least 6 months after stopping treatment.

Fludara Two must not be administered to patients who are pregnant because animal studies and limited experience in humans have shown a possible risk of abnormalities in the unborn baby.

Breast-feeding:
Do not breast feed during your treatment with this medicine. It is not known if this medicine appears in the breast milk of women treated with Fludara Two. However, in animal studies fludarabine phosphate was found in breast milk.

Driving and using machines:
The effect of treatment with Fludara Two on the patient's ability to drive or operate machinery has not been evaluated.

3. HOW TO USE FLUDARA TWO

Fludara Two should be administered under the supervision of a qualified doctor experienced in the use of anti-cancer therapy.

- For information for preparation of the reconstituted or diluted solution, see section 6. Further information / information for medical or healthcare professionals.

How Fludara Two is given:
Fludara Two is given in the form of a solution as an injection or, mostly, as an infusion.

An infusion means that the medicine is given directly into the blood stream by a drip through a vein. One infusion takes approximately 30 minutes.

Your doctor will make sure that Fludara Two is not given beside the vein (paravenously). However, if this happened, no severe local adverse events have been reported.

How much Fludara Two is given:
The dose you are given depends on your body surface area. This is measured in square metres (m^2), and is worked out by your doctor from your height and weight.

The recommended dose is 25 mg fludarabine phosphate/m^2 body surface area.

If you have kidney problems or are over the age of 70 years , you will have regular blood and/or laboratory tests to check your kidney function. If it is found that your kidneys do not work properly you may be given this medicine at a reduced dose. If your kidney function is severely reduced you will not be given this medicine at all (see also section 'Do not use Fludara Two').

The dosage may be decreased if side effects are a problem.

For how long Fludara Two is given:
The dose will be given once a day for 5 consecutive days.
This 5-day course of treatment will be repeated every 28 days until your doctor has decided that the best effect has been achieved (usually after 6 courses).

The duration of treatment depends on how successful your treatment is and how well you tolerate Fludara Two, the repeat course may be delayed if side effects are a problem.

If any Fludara Two solution is accidentally spilt:
If any of the Fludara solution comes into contact with your skin or the lining of your nose or mouth, wash the area thoroughly with soap and water. If the solution gets into your eyes, rinse them thoroughly with plenty of tap water. Avoid any exposure by inhalation.

If more Fludara Two is given than it should:
If you may have received an overdose your doctor will stop the therapy and treat the symptoms. Symptoms of an overdose can be delayed blindness, coma and death due to irreversible toxicity to the central nervous system.
High doses can also lead to a severely reduced number of blood cells.

If a dose of Fludara Two is forgotten:
Your doctor will set the times at which you are to receive this medicine. If you think you may have missed a dose, contact your doctor as soon as possible.

If the treatment with Fludara Two is stopped earlier:
Your doctor may decide together with you to stop your treatment with Fludara if the side effects are becoming too severe.

- If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fludara Two can cause side effects, although not everybody gets them.

Tell your doctor if you notice any unwanted effect, especially if severe or persistent, or if there is a change in your health that you think might be caused by the medicine.

If you are not sure what the adverse reactions below are, ask your doctor to explain them to you.

- **The most common side effects for Fludara Two include:** reduction in blood cell production by the bone marrow which may result in a reduced number of blood cells (*anaemia, neutropenia, and thrombocytopenia*), leading to abnormal bleeding or bruising and infections; infections include inflammation of the lungs which can lead to breathing difficulties (*pneumonia*) and may be serious; fever; feeling sick (*nausea*); vomiting and diarrhoea.
- **Other commonly reported side effects include:** fatigue; weakness; inflammation of the inside of the mouth (*stomatitis*); generally feeling unwell; severe loss of appetite leading to weight loss (*anorexia*); swelling due to excessive fluid retention in parts of the body (*oedema*); chills; numbness or weakness in limbs (*peripheral neuropathy*); disturbed vision and skin rashes.

As a result of serious side effects even death has been reported.

Below we list possible side effects by the parts of the body that may be affected and by how common they are. The rare side effects (less than 10 in every 10,000 patients) were mainly identified from the postmarketing experience.

Common: means between 1 and 10 in every 100 patients are likely to get these.
Uncommon: between 1 and 10 in every 1,000 patients are likely to get these.
Rare: less than 10 in every 10,000 patients are likely to get these.

Whole body
Common: infection; fever; feeling tired (*fatigue*); weakness; general feeling unwell; chills.

Blood production and lymphatic system
Uncommon: autoimmune phenomena (see section ‘Take special care’).
Rare: myelodysplastic syndrome.

- In a small percentage of cancer patients treated with Fludara other types of cancer have developed thatrelate to the blood (*myelodysplastic syndrome (MDS)*). The majority of patients with this cancer were previously, or at the same time or later treated with cytotoxic drugs (alkylating agents) or irradiation. It is well known that in such cases there is a risk for secondary cancers. If Fludara Two was given as the only therapy, development of MDS was not increased.

- A reduction in the number of blood cells has been reported in most patients treated with Fludara Two. Such reduction may be severe and can increase with time during Fludara Two treatment.
This may also lead to an increased risk of (serious) infections, caused by organisms, that usually do not cause disease in healthy persons (including a late reactivation of viruses, e.g. herpes zoster).

- **If you notice any unusual bruising, more bleeding than usual after injury or if you seem to be catching a lot of infections,** tell your doctor immediately.

Metabolic and nutritional disorders
Common: swelling due to excessive fluid retention in parts of the body (*oedema*).
Uncommon: tumour lysis syndrome (see below); changes in levels of the liver or pancreas enzymes.

- If your disease is very severe, your body may not be able to clear all the waste products from the cells destroyed by Fludara Two (tumour lysis syndrome). This may cause kidney failure and heart problems.
  - **If you notice any pain in your side, blood in your urine, or reduced amount of urine,** tell your doctor immediately.

Nervous system
Common: numbness or weakness in limbs (*peripheral neuropathy*).
Uncommon: confusion.
Rare: coma; agitation; seizures.

Special senses
Common: disturbed vision.
Rare: inflammation or damage of the optic nerve (*optic neuritis; optic neuropathy*); blindness.

Respiratory system
Common: inflammation of the lungs which can lead to breathing difficulties (pneumonia).
Uncommon: hypersensitivity reactions of the lungs (*pulmonary infiltrates/pneumonitis/fibrosis*) associated with shortness of breath (*dyspnoea*) and cough.
  - **If you experience any difficulty in breathing, have a cough, or have chest pain,** tell your doctor immediately.

Digestive system
Common: disturbances of the stomach or intestines (*gastrointestinal tract*) such as feeling sick (*nausea*), vomiting, diarrhoea; inflammation of the inside of the mouth (*stomatitis*); severe loss of appetite leading to weight loss (*anorexia*).
Uncommon: bleeding in the stomach or intestines (mainly due to a low platelet count (*thrombocytopenia*)).

Heart and blood vessels
Rare: heart failure; irregular heart beat (*arrhythmia*).
  - **If you have palpitations (if you suddenly become aware of your heart beat) or chest pain,** tell your doctor immediately.

Urinary and reproductive system
Rare: inflammation of the bladder, which can cause pain when passing urine, and can lead to blood in the urine (*haemorrhagic cystitis*).

Skin and appendages
Common: skin rashes.
Rare: skin and/or mucous membrane reaction with redness, inflammation, blistering and erosion (Stevens-Johnson syndrome or a toxic epidermal necrolysis (Lyell's syndrome)).

- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FLUDARA TWO

Keep out of the reach and sight of children.
Do not use Fludara Two after the expiry date which is stated on the carton and vial.

- *Storage of Fludara Two as packed for sale*

This medicinal product does not need any special storage conditions.

- *Storage of Fludara Two after reconstitution*

For information see section 6. Further information, information for medicinal and healthcare professionals.

6. FURTHER INFORMATION

What Fludara Two contains:

- **The active substance is** fludarabine phosphate.

- **The other ingredients are** mannitol and sodium hydroxide.

The powder of Fludara Two is provided in 10-ml glass vials. Each vial contains 50 mg fludarabine phosphate. 1 millilitre of reconstituted solution contains 25 mg fludarabine phosphate.

What Fludara Two looks like and contents of the pack:

Fludara Two is a sterile white to off-white powder for solution for injection or infusion. The powder is reconstituted with water for injection and further diluted.
The reconstituted solution is clear and colourless.

Fludara Two is available in packs containing 5 vials.

The Marketing Authorisation Holder and the Manufacturer:

Marketing Authorisation Holder:
[To be completed nationally]

Manufacturer:
Intendis Manufacturing S.p.A, Milan, Italy

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria	Fludarabinphosphat 50 mg Pulver zur Herstellung einer Injektions- oder Infusionslösung
Belgium	Fludarabine Phosphate Schering 50 mg powder for solution for injection or infusion
Denmark	Fludarabinphosphat "Schering"
Finland	Fludarabine Phosphate Schering
France	Fludarabine Phosphate Schering 50 mg, poudre pour solution injectable ou perfusion
Germany	Fludarabinphosphat 50 mg Pulver zur Herstellung einer Injektions- oder Infusionslösung
Greece	Fludarabine Phosphate / Schering
Italy	Fludarabina Fosfato 50 mg polvere per soluzione iniettabile o per infusione
Ireland	Fludarabine Phosphate 50 mg powder for solution for injection or infusion
Luxembourg	Fludarabine Phosphate 50 mg powder for solution for injection or infusion
Portugal	Fludarabina Lusal
Spain	Fludarabina Fosfato, Schering España, 50 mg polvo para solución inyectable o perfusión
Sweden	Fludarabin Schering

The Netherlands	Fludarabinefosfaat 50 mg, poeder voor oplossing voor injectie/infusie
United Kingdom	Fludara Two 50 mg powder for solution for injection or infusion

This leaflet was last approved in:
[To be completed nationally]

THE FOLLOWING INFORMATION IS INTENDED FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY:

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

Instructions for use, handling and disposal of Fludara Two:

- Reconstitution

Fludara Two should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2 ml of sterile water for injection, the powder should fully dissolve in 15 seconds or less. Each ml of the resulting solution will contain 25 mg of fludarabine phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. The pH range for the final product is 7.2 - 8.2.

- Dilution

The required dose (calculated on the basis of the patient's body surface area) is drawn up into a syringe. For intravenous bolus injection this dose is further diluted in 10 ml of 0.9 % sodium chloride. Alternatively, for infusion, the required dose may be diluted in 100 ml of 0.9 % sodium chloride and infused over approximately 30 minutes.
In clinical studies, the product has been diluted in 100 ml or 125 ml of 5 % dextrose injection or 0.9 % sodium chloride.
The solution must not be mixed with other drugs.

- Storage of Fludara Two after reconstitution

Chemical and physical in-use stability after reconstitution has been demonstrated for 7 days at 4 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, inuse storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 to 8 °C or 8 hours at room temperature.

- Inspection prior to use

The reconstituted solution is clear and colourless. It should be visually inspected before use.
Only clear and colourless solutions without particles should be used. Fludara Two should not be used in case of a defective container.

- Handling and disposal

Fludara Two should not be handled by pregnant staff.
Procedures for proper handling should be followed according to local requirements for cytotoxic drugs.

Caution should be exercised in the handling and preparation of the Fludara Two solution.

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

The medicinal product is for single use only.
Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.
Any unused product or waste material should be disposed of in accordance with local requirements.

Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CONTAINER

1. NAME OF THE MEDICINAL PRODUCT

Fludara Two 50 mg powder for solution for injection or infusion
Fludarabine phosphate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 25 mg fludarabine phosphate when reconstituted.

3. LIST OF EXCIPIENTS

Excipients: Mannitol, sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection or infusion.
One vial contains 50 mg fludarabine phosphate.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after reconstitution and dilution.
Single use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic. Procedures for proper handling should be followed according to local requirements for cytotoxic drugs.

8. EXPIRY DATE

EXP (MM/YYYY)

Reconstituted Fludara Two should be used immediately or within 8 hours of reconstitution if stored at room temperature or within 24 hours if stored at 2 to 8°C.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Fludara Two 50 mg powder for solution for injection or infusion
Fludarabine phosphate
Intravenous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP {MM/YYYY}

Reconstituted Fludara Two should be used immediately or within 8 h (stored at room temp.) or within 24 h (stored at 2-8°C).

4. BATCH NUMBER

LOT

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

25 mg per ml. 50 mg per vial.

6. OTHER

Cytotoxic.

Module 5

Scientific Discussion during Initial Procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA has granted a marketing authorisation for Fludara Two 50 mg Powder for Solution for Injection for Infusion, from Schering Healthcare Limited for the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves.

This informed consent application was made under Article 10c [formerly Article 10.1(a)(i) of directive 2001/83/EC, as amended]. It is an informed consent application making reference to the original Fludara product (PL 00053/0239) granted authorisation in the UK on 11th August 1994.

Fludara Two contains fludarabine phosphate, a water-soluble fluorinated nucleotide analogue of the antiviral agent vidarabine, 9-ß-D-arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase.

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

While some aspects of the mechanism of action of 2F-ara-ATP are as yet unclear, it is assumed that effects on DNA, RNA and protein synthesis all contribute to inhibition of cell growth with inhibition of DNA synthesis being the dominant factor. In addition, in vitro studies have shown that exposure of CLL lymphocytes to 2F-ara-A triggers extensive DNA fragmentation and cell death characteristic of apoptosis.
No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on duplicate application to a product that has been licensed for over 10 years.

The RMS has also been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation. For manufacturing sites within the community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

With the UK as Reference Member State in this Mutual Recognition Procedure (MRP), the marketing authorisation holder (Schering Healthcare Limited) gained approval for marketing

authorisations in Austria, Belgium, Germany, Denmark, Greece, Spain, Sweden, Finland, France, Ireland, Italy, Luxembourg, The Netherlands and Portugal.

Fludara Two is a Prescription Only Medicine (POM).

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Fludara Two 50 mg Powder for Solution for Injection for Infusion
Name of the active substance	Fludarabine Phosphate
Pharmacotherapeutic classification (ATC code)	L01B B05
Pharmaceutical form and strength	Powder for Solution for Injection or Infusion; 50mg per vial
Reference numbers for the Mutual Recognition Procedure	UK/H/0817/001
Reference Member State	United Kingdom
Member States concerned	Austria, Belgium, Germany, Denmark, Greece, Spain, Finland, France, Ireland, Italy, Luxembourg, The Netherlands and Portuga
Name and address of manufacturer responsible for batch release in the EEA	Schering AG Mullerstrasse 170-178 D-13353 Berlin Germany
Date of first authorisation	27th April 2005
Marketing Authorisation Number(s)	PL 00053/0347
Date of assessment report	28th October 2005
Authorisation holder's name and address	Schering Healthcare Limited The Brow, Burgess Hill West Sussex, RH15 9NE United Kingdom

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 INTRODUCTION AND REGULATORY BACKGROUND

This is a Marketing Authorisation Application for a duplicate licence for Fludara, first granted in the UK on 11th August 1994 (PL 00053/0239) following a CPMP Concertation Procedure (No.55).
Fludara i.v. was first approved in the US in 1991 and following UK approval in 1994, went through the Mutual Recognition (MR) procedure in 1999 (UK/H/055/01), with the UK acting as RMS.
It is now approved in more than 80 countries for the second line treatment of CLL.

In 2002, the indications were extended to include initial treatment of patients with CLL.

There was a recent Mutual Recognition renewal application assessed for the original Fludara application [UK/H/055/01]. The application was approved and finalised in February 2005.

There have been no regulatory actions taken for safety reasons.

Marketing Authorisation was granted in the UK on 27th April 2005 for the current Fludara Two application (PL 00053/0347), which was submitted under Article 10.1(a)(i) of Directive 2001/83/EC, as amended, as an informed consent application making reference to the original Fludara product. This MRP (UK/H/817/01) is intended for approval of the duplicate licence in selected EU countries where the original product is already licensed.

III.2 REVIEW AND CONCLUSION

The dossier has been compiled in accordance with the MRFG document "Informed consent applications in Mutual Recognition Procedures – Recommendations" The applicant has submitted Modules 1, 2 and 3 only. With reference to the MRFG document mentioned, part III and /or Part IV data for the original product can be referred to. The CMC part, Module 3, of the dossier has been updated to the CTD format.

A signed declaration is provided that the content and data of the Quality Module 3 is identical to the current approved Quality part of Fludara (including approved variations since grant of the original authorisation), and there has been no changes to the dossier as a result of the reformatting except corrections of typographical errors and editorial rewording. A Quality Overall Summary is provided.

The applicant has confirmed that the data approved for the currently licensed Fludara in the member states they are applying to be identical to that to be submitted with this new application. Therefore it is intended that for the purposes of this MRP (UK/H/817/01), the member states are asked to refer to data approved for the previous submission (UK/H/055/01).

It is recommended that a Marketing Authorisation should, therefore, be granted.

III.3 PRE-CLINICAL ASPECTS

This is a standard abridged informed consent application for Fludara Two, a duplicate for Fludara (PL 00053/0239) granted authorisation in the UK in 1994. Following UK approval in 1994, Fludara first went through the MR procedure in 1999 (UK/H/055/01), with the UK acting as RMS.

It is now approved in more than 80 countries for the second line treatment of CLL.

No new preclinical data have been submitted nor are required for this application.

For further preclinical information relevant to this product.

III.3 CLINICAL ASPECTS

III.3.1 Clinical Pharmacology

Pharmacodynanics and Pharmacokinetics

Fludarabine phosphate is an antineoplastic agent developed for use in the treatment of B cell chronic lymphocytic leukaemia, either as first or second line therapy.

The applicant has not submitted any new data on clinical pharmacodynamics and pharmacology of fludarabine phosphate and none are required as per Article 10c. The reader is asked to refer to sections 5.1 and 5.2 of the Summary of Product Characteristics (pages 9 and 10 of Public Assessment Report) where a summary of current knowledge on pharmacodynamics and pharmacokinetics of fludarabine phosphate respectively is provided.

III.3.2 Clinical Efficacy

No new efficacy data were submitted by the applicant. The documented clinical efficacy of the active remains satisfactory for the claimed indications and the proposed dosages.

III.3.3 Clinical Safety

No new safety data were submitted with the application. The recorded safety profile of the active remains satisfactory when used in the claimed indications and at the recommended dosages.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

This informed consent application was made under Article 10c [formerly Article 10.1(a)(i) of directive 2001/83/EC, as amended], making reference to the original Fludara product (PL 00053/0239) granted authorisation in the UK on 11th August 1994.

No new efficacy or safety data have been included in the dossier and none are necessary for an informed consent application.

It is accepted that risk:benefit ratio is favourable.

The product literature has been amended in-line with the current guidelines. The SPC includes all relevant warnings.

There are no pre-clinical concerns with this application or with the clinical use of fludarabine phosphate.