Approved Professional Information for FLUDARA

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

FLUDARA sterile lyophilised solid cake for solution

FLUDARA ORAL film coated tablet

COMPOSITION

FLUDARA:

Active ingredient:

Each vial contains 50 mg fludarabine phosphate as a lyophilised solid cake (equivalent to 39,05 mg fludarabine per vial).

Inactive ingredients:

Mannitol, sodium hydroxide (less than 1 mmol sodium).

Contains sugar (50 mg mannitol per vial).

FLUDARA ORAL:

Active ingredient:

Each film coated tablet contains 10 mg fludarabine phosphate.

Inactive ingredients:

Colloidal silicon dioxide, croscarmellose sodium, ferric oxide red, ferric oxide yellow, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, talc and titanium dioxide.

Contains sugar (74,75 mg lactose monohydrate per tablet).

CATEGORY AND CLASS

A. 26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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

Fludarabine phosphate is dephosphorylated to 2-fluoro-ara-A which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-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 2-fluoro-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 vitro studies have shown that exposure of chronic lymphocytic leukaemia lymphocytes to 2F-ara-A triggers extensive DNA fragmentation and cell death characteristic of apoptosis.

A randomised trial of **FLUDARA** 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** compared to CAP (45 % vs 26 % and 13 % vs 6 % respectively); response duration and overall survival were similar with **FLUDARA** and CAP. Within the stipulated treatment period of 6 months the number of deaths was 9 (**FLUDARA**) vs 4 (CAP). Post-hoc analyses using only data of up to 6 months after start of treatment revealed a difference in survival curves of **FLUDARA** and CAP in favour of CAP in the subgroup of pretreated Binet stage C patients.

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, short-term infusion and following continuous infusion of fludarabine phosphate (**FLUDARA**, 2F-ara-AMP). 2F-ara-A demonstrated a similar pharmacokinetic profile in chronic lymphocytic leukaemia.

No clear correlation was found between 2F-ara-A 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 and metabolism

2F-ara-AMP is a water-soluble prodrug of fludarabine (2F-ara-A), which is dephosphorylated in the human organism to the nucleoside 2F-ara-A. Another metabolite, 2F-ara-hypoxanthine, which represents the major metabolite in the dog, was only observed in humans to a minor extent.

After single dose infusion of 25 mg 2F-ara-AMP per m^2 to chronic lymphocytic leukaemia patients for 30 minutes, 2F-ara-A reached mean maximum concentrations in the plasma of 3,5 to 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 to 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. Post maximum levels decayed in three disposition phases with an initial half-life of approximately 5 minutes, an intermediate half-life of 1 to 2 hours and a terminal half-life of approximately 20 hours.

An interstudy comparison of 2F-ara-A pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 ml/min/m^2 (2,2 ml/min/kg) and a mean volume of distribution (V_{ss}) of 83 l/m^2 (2,4 l/kg). Data showed a high inter-individual variability. After intravenous administration of fludarabine phosphate, 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.

After peroral fludarabine phosphate doses, maximum 2F-ara-A plasma levels reached approximately 20 to 30 % of corresponding IV levels at the end of infusion and occurred 1 to 2 hours post dose. The mean systemic 2F-ara-A availability was in the range of 50 to 65 % following single and repeated doses and was similar after ingestion of a solution or immediate release tablet formulation. After a peroral dose of 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 2F-ara-A and a delayed time of occurrence of C_{max} were observed; terminal half-lives were unaffected.

Elimination

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

Characteristics in patients

Individuals with impaired renal function exhibited 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 chronic lymphocytic leukaemia patients were observed at a median of 4 hours and exhibited a considerable variation, with a median peak

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

Lactation

There is evidence from preclinical data after intravenous administration to rats that **FLUDARA** and/or metabolites transfer from maternal blood to milk. In a pre/postnatal developmental toxicity study fludarabine phosphate was intravenously administered to rats during late gestation and the lactation period at dose levels of 1, 10 and 40 mg/kg/day. The offspring of the high dose group showed a decrease in body weight gain and viability and a delay in skeletal maturation on day 4 postpartum. However, it should be taken into account that the dosing period covered also the late prenatal development (see **HUMAN REPRODUCTION**).

INDICATIONS

FLUDARA is indicated for the initial treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) and for patients with CLL with sufficient bone marrow reserve who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating agent-containing regimen.

CONTRAINDICATIONS

FLUDARA is contraindicated in those patients who are hypersensitive to fludarabine or its components, in renally impaired patients with creatinine clearance < 30 ml/minute and in patients with haemolytic anaemia.

The safety and effectiveness of **FLUDARA** in children have not been established.

WARNINGS AND SPECIAL PRECAUTIONS

Neurotoxicity

When used at high doses in dose-ranging studies in patients with acute leukaemia, **FLUDARA** was associated with severe neurological effects, including blindness, coma and death. This severe central nervous system toxicity occurred in 36 % of patients treated intravenously with doses approximately four times greater (96 mg/m^2/day for 5 to 7 days) than the dose recommended for treatment of chronic lymphocytic leukaemia. In patients treated at doses in the range of the dose recommended for chronic lymphocytic leukaemia, severe central nervous system toxicities including coma, seizures, agitation and confusion have occurred.

In post-marketing experience neurotoxicity has been reported to occur earlier (one week) or later than in clinical trials (up to 7 months).

Patients should be closely observed for signs of neurological side effects.

The effect of chronic administration of **FLUDARA** on the central nervous system is unknown.

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,
  - or when **FLUDARA** is given in patients with other risk factors such as cranial or total body irradiation, haematopoietic 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 and 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 utilising MRI. If the diagnosis is confirmed, **FLUDARA** should be permanently discontinued.

Impaired state of health

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

Impaired hepatic function

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 perceived benefit outweighs any potential risk.

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 to 25 days) for granulocytes and 16 days (range 2 to 32 days) for platelets. Most patients had haematological 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 an antineoplastic medicine with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of haematological and non-

haematological toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anaemia, neutropenia and thrombocytopenia.
Several instances of trilineage bone marrow hypoplasia or aplasia resulting in pancytopenia, sometimes resulting in death, have been reported in adult patients. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated and untreated patients.

Disease progression

Disease progression and transformation (e.g. Richter's syndrome) have been commonly reported in chronic lymphocytic leukaemia.

Transfusion of blood products

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** treated patients. Fatal outcome as a consequence of this disease has been reported with a high frequency. Therefore, to minimize the risk of transfusion-associated graft-versus-host disease, patients who require blood transfusion and who are undergoing, or who have received, treatment with **FLUDARA** should receive irradiated blood only.

Skin cancer

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

Tumour lysis syndrome

Tumour lysis syndrome associated with **FLUDARA** treatment has been reported uncommonly in 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, the occurrence of life-threatening and sometimes fatal autoimmune phenomena (e.g. autoimmune haemolytic anaemia, autoimmune thrombocytopenia, thrombocytopenic purpura, pemphigus, Evans syndrome) have been reported during or after treatment with **FLUDARA**. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after re-challenge with **FLUDARA**.

Patients undergoing treatment with **FLUDARA** 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** is recommended in case of haemolysis. Blood transfusion (irradiated, see above) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.

Renal impairment

The total body clearance of the principal plasma metabolite 2F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. Patients with reduced renal function demonstrated an increased total body exposure (AUC of 2F-ara-A). Limited clinical data are available in patients with impairment of renal function (creatinine clearance below 70 ml/minute).

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** treatment is contraindicated if creatinine clearance is < 30 ml/minute.

Elderly patients

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.

In patients aged 65 years or older, creatinine clearance should be measured before start of treatment, see ***Reduced renal function*** and **DOSAGE AND DIRECTIONS FOR USE**.

Vaccination

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

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 because most patients who have been resistant to **FLUDARA** have shown resistance to chlorambucil.

Excipients

Each vial of **FLUDARA** 50 mg powder for solution for injection/infusion contains less than 1 mmol sodium (23 mg), essentially “sodium free”.

Each vial of **FLUDARA** 50 mg powder for solution for injection/infusion contains mannitol, which may have a mild laxative effect.

Each **FLUDARA ORAL** 10 mg film coated tablet contains 74,75 mg lactose monohydrate, which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption e.g. galactosaemia should not take **FLUDARA ORAL**.

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. Reaction can be particularly impaired due to insufficient sleep, individual sensitivity and dosage.

INTERACTIONS

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

The therapeutic efficacy of **FLUDARA** may be reduced by dipyridamole and other inhibitors of adenosine uptake.

Pharmacokinetic parameters after peroral administration were not significantly affected by concomitant food intake.

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

HUMAN REPRODUCTION

Pregnancy

FLUDARA should not be used during pregnancy.

The results from intravenous embryotoxicity studies in rats and rabbits indicated an embryolethal and teratogenic effect at the therapeutic dose. Preclinical data in rats demonstrated a transfer of **FLUDARA** and/or metabolites through the fetoplacental barrier.

There are very limited data of **FLUDARA** use in pregnant women during the first trimester.

FLUDARA has the potential to cause fetal harm.

Lactation

It is not known whether this medicine is excreted in human milk.

However, there is evidence from preclinical data that **FLUDARA** and/or metabolites transfer from maternal blood to milk.

Therefore, breastfeeding should not be initiated during **FLUDARA** treatment. Breastfeeding women should discontinue breastfeeding.

Fertility

Women of childbearing potential must be apprised of the potential hazard to the fetus.

Both sexually active men and women of childbearing potential must take effective contraceptive measures during and at least for 6 months after cessation of therapy.

DOSAGE AND DIRECTIONS FOR USE

General information

Children and adolescents

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

Elderly patients

Since there are limited data for use of **FLUDARA** in elderly persons (> 75 years), caution should be exercised with administration of **FLUDARA** in these patients (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Patients with renal impairment

Doses should be adjusted for patients with reduced kidney function. If creatinine clearance is between 30 and 70 ml/min, the dose should be reduced by up to 50 % and close haematological

monitoring should be used to assess toxicity. For further information see **WARNINGS AND SPECIAL PRECAUTIONS**.

FLUDARA treatment is contraindicated if creatinine clearance is < 30 ml/min.

Patients with hepatic impairment

The safety and efficacy have not been studied in patients with hepatic impairment.

Formulation for intravenous use

FLUDARA should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2 ml of sterile water for injection, the solid cake 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 to 8,2. Reconstituted **FLUDARA** should be used within 8 hours of reconstitution.

Dosage

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

FLUDARA must only be administered intravenously. No cases have been reported in which paravenously administered **FLUDARA** led to severe local adverse reactions. However, unintentional paravenous administration must be avoided.

Adults

The recommended dose is 25 mg/m^2 body surface given daily for 5 consecutive days every 28 days by the intravenous route. Each vial is to be made up in 2 ml water for injection. Each ml of the resulting solution will contain 25 mg fludarabine phosphate. The dose should not be exceeded as severe neurotoxicity may occur.

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

Depending on the treatment success and the tolerability of the medicine, **FLUDARA** should be administered in chronic lymphocytic leukaemia patients up to the achievement of best response (complete or partial remission, usually 6 cycles) and then the medicine should be discontinued.

Handling and disposal

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 medicine. 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.

Tablets for oral use

Dosage

FLUDARA ORAL should be prescribed by a qualified medical practitioner experienced in the use of antineoplastic therapy.

Adults

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

The duration of treatment depends on the treatment success and the tolerability of **FLUDARA**.

In chronic lymphocytic leukaemia patients **FLUDARA** should be administered up to the achievement of best response (complete or partial remission, usually 6 cycles) and then **FLUDARA** should be discontinued.

Handling and disposal

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 medicine. Waste material may be disposed of by incineration.

SIDE EFFECTS

Serious opportunistic infections have occurred in patients treated with **FLUDARA**. Fatalities as a consequence of serious adverse events have been reported. The adverse events below are classified by MedDRA system organ classes (MedDRA SOCs) under the CIOMS headings of frequency, using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000) and unknown.

Infections and infestations

Very common: Infections or opportunistic infections (like latent viral reactivation, e.g. herpes zoster virus, Epstein-Barr virus, progressive multifocal leukoencephalopathy), pneumonia.

Rare: Lymphoproliferative disorder (EBV-associated).

Neoplasms benign and malignant (including cysts and polyps)

Common: 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

Very common: Neutropenia, anaemia, thrombocytopenia.

Common: Myelosuppression.

Immune system disorders

Uncommon: Autoimmune disorder (including autoimmune haemolytic anaemia, thrombocytopenic purpura, pemphigus, Evans syndrome, acquired haemophilia).

Metabolism and nutrition disorders

Common: Anorexia.

Uncommon: Tumour lysis syndrome (including renal failure, hyperkalaemia, metabolic acidosis, haematuria, urate crystalluria, hyperuricaemia, hyperphosphataemia, hypocalcaemia).

Nervous system disorders

Common: Peripheral neuropathy.

Uncommon: Confusion.

Rare: Agitation, seizures, coma.

Eye disorders

Common: Visual disturbance.

Rare: Optic neuritis, optic neuropathy, blindness.

Cardiac disorders

Rare: Heart failure, dysrhythmia.

Vascular disorders

Uncommon: Gastrointestinal haemorrhage.

Respiratory, thoracic and mediastinal disorders

Very common: Cough.

Uncommon: Pulmonary toxicity (including dyspnoea, pulmonary fibrosis, pneumonitis).

Gastrointestinal disorders

Very common: Nausea, vomiting, diarrhoea.

Common: Stomatitis.

Uncommon: Abnormal pancreatic enzymes.

Hepatobiliary disorders

Uncommon: Abnormal hepatic enzymes.

Skin and subcutaneous tissue disorders

Common: Rash.

Rare: Skin cancer, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell type).

General disorders and administration site conditions

Very common: Fever, fatigue, weakness.

Common: Chills, malaise, oedema, mucositis.

Spontaneous reports (frequency unknown)

The following events were identified from post-marketing spontaneous reporting:

Nervous system disorders

Leukoencephalopathy, acute toxic leukoencephalopathy, reversible posterior leukoencephalopathy syndrome (RPLS) (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Vascular disorders

Haemorrhage (including cerebral haemorrhage, pulmonary haemorrhage, haemorrhagic cystitis).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

High doses of **FLUDARA** have been associated with leukoencephalopathy, acute toxic leukoencephalopathy, or reversible posterior leukoencephalopathy syndrome (RPLS). Symptoms may include headache, nausea and vomiting, seizures, visual disturbances such as vision loss, altered sensorium, and focal neurological deficits. Additional effects may include optic neuritis, and papillitis, confusion, somnolence, agitation, paraparesis/ quadriparesis, muscle spasticity, incontinence, irreversible central nervous system toxicity characterised by delayed blindness, coma, and death. High doses are also associated with severe thrombocytopenia and neutropenia due to bone marrow suppression.

There is no known specific antidote for **FLUDARA** overdosage. Treatment consists of discontinuation of treatment and supportive therapy.

IDENTIFICATION

FLUDARA

Sterile white lyophilised solid cake or powder supplied in clear glass single dose vials of 10 ml capacity.

FLUDARA ORAL

Salmon-pink capsule shaped film coated tablets with “LN” in a regular hexagon embossed on one side.

STORAGE INSTRUCTIONS

FLUDARA

Store at or below 30 °C.

KEEP OUT OF REACH OF CHILDREN.

FLUDARA ORAL

Store at or below 30 °C in original package.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

FLUDARA: 28/26/0605

FLUDARA ORAL: 36/26/0422

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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