PACKAGE LEAFLET: INFORMATION FOR THE USER

Fludarabine Phosphate 25 mg/ml concentrate for solution for injection or infusion
fludarabine phosphate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Fludarabine Phosphate 25 mg/ml is and what it is used for

Fludarabine Phosphate 25 mg/ml is a cytotoxic (anti-cancer medicine): medicines that inhibit the growth of cancer cells.

Fludarabine Phosphate 25 mg/ml is used to treat chronic B-cell lymphocytic leukaemia (B-CLL), in patients with sufficient healthy blood cells production. First treatment for chronic lymphocytic leukaemia with fludarabine phosphate should only be started in patients with advanced disease having disease related symptoms or evidence of disease progression.

CLL is a cancer of the white blood cells (called lymphocytes).
If you are diagnosed with CLL, too many lymphocytes are produced. They either don't 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 cells they push aside (displace) healthy blood cells in the bone marrow (where most new blood cells are formed). They also displace the healthy blood cells in the blood and organs. Without enough healthy blood cells, infections, anaemia, bruising, excessive bleeding (haemorrhaging) or even organ failure can result.

2. What you need to know before you use Fludarabine Phosphate 25 mg/ml

Do not use Fludarabine Phosphate 25 mg/ml
- if you are ***allergic*** to fludarabine phosphate or any of the other ingredients of this medicine (listed in section 6).
- if your ***kidney function*** is severely reduced. Your doctor will decide, based on your kidney function whether Fludarabine Phophate 25 mg/ml may or may not be used.
- if you have a specific type of ***anaemia*** (decompensated haemolytic anaemia; this is a shortage of red blood cells). Your doctor will have told you if you have this condition
- if you are ***breastfeeding*** (see also "Pregnancy, breast-feeding and fertility").

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Fludarabine Phophate 25 mg/ml:

- **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 precautions.

- If you feel very unwell, notice any unusual bruising, more bleeding than usual after injury, or if you seem to be catching a lot of infections.
► Tell your doctor if any of these apply, before your treatment.

- If during treatment you have a red to brownish urine, or have a rash or any blisters on your skin.
► Tell your doctor immediately.
These may be signs of a reduction in the number of blood cells, which may be caused either by the disease itself or the therapy. It can last for up to a year, independent of whether or not you had treatment with fludarabine before. During treatment with fludarabine also your immune system may attack different parts of your body, or your red blood cells (called *'autoimmune disorders'*). These conditions can be life-threatening.
If this occurs your doctor will stop your treatment and you may receive further medication such as transfusion of irradiated blood (see below) and adrenocorticoids.
You will have regular blood tests during treatment and you will be closely monitored while you are being treated with fludarabine.

- If you notice any unusual symptoms of your nervous system such as disturbed vision.
► Tell your doctor.
If fludarabine is used for a long time, its effects on the central nervous system are not known. However patients treated with the recommended dose for up to 26 courses of therapy were able to tolerate it. In patients on doses four times greater than recommended blindness, coma and death have been reported. Some of these symptoms appeared delayed around 60 days or more after treatment has been stopped.

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

- If you need to have stem cells collected and you are being treated with fludarabine (or have been).
► Tell your doctor.

- If you need a blood transfusion and you are being treated with fludarabine (or have been).
► Tell your doctor.
In case you need a blood transfusion your doctor will ensure that you only receive blood that has been treated by irradiation. There have been severe complications and even death, from transfusions of non-irradiated blood.

- **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 you have or have had skin cancer** it may worsen or flare up again while fludarabine therapy or afterwards. You may develop skin cancer during or after fludarabine therapy.

Other things to consider, while you are treated with fludarabine:

- **Men and women, who are fertile must use effective contraception**

during treatment and for at least 6 months afterwards. It cannot be ruled out that fludarabine may harm an unborn baby. Your doctor will carefully weigh the benefit of your treatment against a possible risk for an unborn child and, if you are pregnant, will only treat you with fludarabine if clearly necessary.

- **If you consider or are breast-feeding** you should not start it or continue while on treatment with fludarabine.

- **If you need a vaccination, check with your doctor**, because live vaccinations should be avoided during and after treatment with fludarabine.

- **If you have kidney problems or if you are over 65**, you will have regular blood and/or laboratory tests to check your kidney function. If your kidney problems are severe, you will not be given this medicine at all (see also 'Do not use Fludarabine Phosphate 25 mg/ml' and section 3 'How to use Fludarabine Phosphate 25 mg/ml').

- **If you have liver problems,** your doctor should only give you this medicine with caution.

- **If you are over 75 years old**, Fludarabine Phosphate 25 mg/ml will be given with caution.

Children
The safety of this medicine in children has not been established.

Other medicines and Fludarabine Phosphate 25 mg/ml
Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines.

It is especially important to tell your doctor about:
• **pentostatin** *(deoxycoformycin)*, also used to treat B-CLL. Taking these two drugs together can lead to severe lung problems
• **dipyridamole**, used to prevent excessive blood clotting or other similar substances. They may reduce the effectiveness of fludarabine
• **cytarabine** (*Ara-C*) used to treat chronic lymphatic leukaemia. If fludarabine is combined with cytarabine, levels of the active form of fludarabine in leukaemic cells may rise. However, the overall levels in the blood and its elimination from the blood were not shown to have changed.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

You should not be given Fludarabine Phosphate 25 mg/ml if you are pregnant, because animal studies and limited experience in humans have shown a possible risk of abnormalities in the developing foetus. If you are a woman who may still be fertile, you must avoid becoming pregnant. However, if you do become pregnant inform your doctor immediately, (see also "Other things to consider, while you are treated with fludarabine").
Men and women who may still be fertile must use a reliable form of contraception during and for at least 6 months after stopping treatment.

It is not known if fludarabine appears in the breast milk of women treated with this medicine. However, in animal studies fludarabine has been found in breast milk. Therefore you should not breast feed during your treatment with this medicine.

Driving and using machines
Fludarabine may reduce the ability to drive and use machines, since e.g. tiredness, weakness, visual disturbances, confusion, agitation and seizures have been observed.

Fludarabine Phosphate 25 mg/ml contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'.

3. How to use Fludarabine Phosphate 25 mg/ml

Carefully follow the advice of your doctor when using Fludarabine Phosphate 25 mg/ml. Your doctor will decide when and how long Fludarabine Phosphate 25 mg/ml will be given to you.

Fludarabine Phosphate 25 mg/ml should be used under the supervision of a qualified doctor experienced in the use of anticancer therapy.

For Instructions on dilution, handling and disposal see "The following information is intended for healthcare professionals only" at the end of this leaflet.

The administered amount of Fludarabine Phosphate 25 mg/ml (the dose) depends on the size of your body. Technically this is measured in square metres (m^2), but actually is calculated from your height and weight.

General guidance
The recommended dose is 25 mg/m^2 body surface per day. This will be given either as an injection or as an infusion for 5 consecutive days. This five day course of treatment will be repeated every 28 days until your doctor has decided that the best possible effect has been achieved. In general this is after 6 cycles, in other words after approximately 6 months. The dosage may be decreased or the repeat course delayed if side effects are a problem.
If you have kidney problems you will receive a reduced dose and you will have regular blood tests.

If you received too much Fludarabine Phosphate 25 mg/ml
There is no specific antidote for Fludarabine Phosphate 25 mg/ml overdosage. If you received too much Fludarabine Phosphate 25 mg/ml, the doctor will stop the therapy and treat the symptoms.
High doses of Fludarabine Phosphate 25 mg/ml have been associated with irreversible central nervous system side effects characterised by delayed blindness, coma, and death.
High doses are also associated with severe reduction in the number of certain types of blood cells (severe thrombocytopenia (decreased number of platelets attended with bruises and bleeding) and neutropenia (decreased number of white blood cells attended with increased infection risk)) due to decreased activity of the bone marrow (bone marrow suppression).

If administration of Fludarabine Phosphate 25 mg/ml 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 you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you are not sure what the adverse reactions below are, ask your doctor to explain them to you.
Some side effects can be life-threatening.

- If you have difficulty breathing, have a cough, or have chest pain with or without fever. These may be signs of an infection of the lungs.

- If you notice any unusual bruising, more bleeding than usual after injury or if you seem to be catching a lot of infections. These may be caused by a reduced number of blood cells. This may also lead to an increased risk of (serious) infections, caused by organisms, that usually do not cause disease

in healthy persons *(opportunistic infections)* including a late reactivation of viruses, for example herpes zoster.

- If you notice any pain in your side, blood in your urine, or reduced amount of urine. These may be signs of *tumour lysis syndrome* (see section 2 under 'Warnings and precautions').

- If you notice any skin and / or mucous coat reaction with redness, inflammation, blistering and tissue break down. These may be signs of a severe allergic reaction (*Lyell's syndrome, Stevens-Johnson syndrome)*.

- If you have palpitations (if you suddenly become aware of your heart beat) or chest pain. These may be signs of heart problems.

► Tell your doctor immediately, if you notice any of these effects.

Below we list possible side effects by how common they are. The rare side effects (may affect up to 1 in 1,000 people) were mainly identified from post-marketing experience.

• **Very common** (may affect more than 1 in 10 people):

- infections (some serious);
- infections due to depressed immune system (*opportunistic infections);*
- infection of the lungs *(pneumonia)* with possible symptoms like breathing difficulties and/or cough with or without fever;
- reduction in the number of blood platelets *(thrombocytopenia)* with the possibility of bruising and bleeding*;*
- lowered white blood cell count (*neutropenia*);
- lowered red blood cell count (*anaemia*);
- cough;
- vomiting, diarrhoea, feeling sick *(nausea);*
- fever;
- feeling tired *(fatigue)*;
- weakness.

• **Common** (may affect up to 1 in 10 people):

- other blood related cancers *(myelodysplastic syndrome, acute myeloid leukaemia*. Most patients with these conditions were previously, or at the same time or later treated with other cancer drugs (*alkylating agents, topoisomerase inhibitors)* or radiation therapy);
- bone marrow depression *(myelosuppression)*;
- severe loss of appetite leading to weight loss (*anorexia*);
- numbness or weakness in limbs (*peripheral neuropathy*);
- disturbed vision;
- inflammation of the inside of the mouth *(stomatitis)*;
- skin rash;
- swelling due to excessive fluid retention (*oedema*);
- inflammation of the mucous coat of the digestive system from the mouth to the anus (*mucositis*);
- chills;
- generally feeling unwell.

• **Uncommon** (may affect up to 1 in 100 people):

- autoimmune disorder (see section 2 under 'Warnings and precautions');
- tumour lysis syndrome (see section 2 under 'Warnings and precautions');
- confusion;

- lung toxicity; scaring throughout the lungs *(pulmonary fibrosis)*, inflammation of the lungs *(pneumonitis)*, shortness of breath *(dyspnoea)*;
- bleeding in the stomach or intestines;
- abnormal levels of the liver or pancreas enzymes.

• **Rare** (may affect up to 1 in 1,000 people):

- disorders of the lymph system due to a viral infection *(EBV-associated lymphoproliferative disorder)*;
- coma;
- seizures;
- agitation;
- blindness;
- inflammation or damage of the nerve of the eyes (*optic neuritis; optic neuropathy*);
- heart failure;
- irregular heart beat (*arrhythmia*);
- skin cancer;
- skin and/or mucous coat reaction with redness, inflammation, blistering and tissue break down (*Lyell's syndrome, Stevens-Johnson syndrome);*

• **Not known** (frequency cannot be estimated from the available data):

- Inflammation of the bladder, which can cause pain when passing urine, and can lead to blood in the urine (*haemorrhagic cystitis*);
- Bleeding of the lungs (pulmonary haemorrhage);
- Bleeding into brain tissue (cerebral haemorrhage).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.
Website: www.hpra.ie; E-mail: medsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Fludarabine Phosphate 25 mg/ml

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Fludarabine Phosphate 25 mg/ml contains
- The active substance is fludarabine phosphate.
  1 ml of concentrate contains 25 mg fludarabine phosphate.
  Each vial of 2 ml contains 50 mg fludarabine phosphate.
- The other ingredients are mannitol (E421), sodium hydroxide (E524, for pH adjustment) and water for injections.

What Fludarabine Phosphate 25 mg/ml looks like and contents of the pack
Fludarabine Phosphate 25 mg/ml is a clear, colourless or slightly brownish-yellow solution, essentially free from particles, in a colourless glass vial with rubber stopper, aluminium seal and plastic snap-cap. Each pack contains one vial.

Manufacturer
Pharmachemie B.V.
Swensweg 5
PO Box 552
2003 RN Haarlem, the Netherlands

Marketing Authorisation Holder
Pharmachemie B.V.
Swensweg 5
2031 RN Haarlem
The Netherlands

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

Belgium	Fludarabine Teva 25 mg/ml, concentraat voor oplossing voor injectie/infusie
Czech Rep.	Fludarabine-Teva 25mg/ml, koncentrát pro přípravu injekčního nebo infuzního roztoku
Germany	Fludarabinphosphat-GRY 25mg/ml Konzentrat zur Herstellung einer Injektionslösung oder Infusionslösung
Denmark	Fludarabinphosphat "Pharmachemie" 25 mg/ml, koncentrat til injektionsvaeske og infusionsvæske, opløsning
Greece	FLUDARABINE/TEVA, Πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση, 25 mg/ml
Spain	Fludarabina TEVA 25mg/ml concentrado para solución para perfusión o inyección EFG
France	Fludarabine - Teva 25 mg/ml, solution à diluer pour injectable ou perfusion.
Ireland	Fludarabine Phosphate 25 mg/ml concentrate for solution for injection or infusion
Italy	Fludarabina -Teva 25 mg/ml, - concentrato per soluzione iniettabile o per infusione
Luxembourg	Fludarabine Teva 25 mg/ml, solution à diluer pour injectable ou perfusion
Netherlands	Fludarabinefosfaat – PCH 25 mg/ml, concentraat voor oplossing voor infusie of injectie
Poland	Fludarabine Teva
Slovenia	Fludarabin Teva 25 mg/ml, koncentrat za raztopino za injiciranje ali infundiranje
United Kingdom	Fludarabine phosphate 25 mg/ml, concentrate for solution for injection or infusion

This leaflet was last revised in 05/2016

The following information is intended for healthcare professionals only:

Instructions on dilution, handling and disposal

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned below.

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, fludarabine has been diluted in 100 ml or 125 ml of 5% dextrose injection or 0.9% sodium chloride.

Inspection prior to use

Only clear and colourless solutions without particles should be used. The product should not be used in case of a defective container.

Storage after dilution

Chemical and physical in-use stability of the solution prepared for injection or infusion has been demonstrated as:

Storage in	Medium	Concentration	Stability for
Non-PVC bag	0.9% sodium chloride	0.3 - 6 mg/ml	5 days in a refrigerator (2 °C - 8 °C) or at ambient temperature/light
	5% glucose	0.3 - 6 mg/ml	5 days in a refrigerator (2 °C - 8 °C) or at ambient temperature/light
Glass bottle	0.9% sodium chloride	0.3 - 6 mg/ml	5 days in a refrigerator (2 °C - 8 °C) or at ambient temperature/light
	5 % glucose	0.3 mg/ml	5 days in a refrigerator (2 °C - 8 °C) or at ambient temperature/light
		6 mg/ml	5 days in a refrigerator (2 °C - 8 °C) or 3 days at ambient temperature/light

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Handling and disposal

Fludarabine 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 of the fludarabine 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 medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.