Package leaflet: Information for the user

Fludarabine phosphate 25 mg/ml, concentrate for solution for injection/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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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 contains the active substance fludarabine phosphate which stops the growth of new cancer cells. All cells of the body produce new cells like themselves by dividing. Fludarabine phosphate 25 mg/ml is taken up by the cancer cells and stops them dividing.

In cancers of the white blood cells (such as chronic lymphocytic leukaemia), the body produces many abnormal white blood cells (lymphocytes) and lymph nodes start to grow in various parts of the body. The abnormal white blood cells cannot carry out the normal disease fighting functions and may push aside healthy blood cells. This can result in infections, a decrease in number of red blood cells (anaemia), bruising, severe bleeding or even organ failure. Fludarabine Phosphate 25 mg/ml is used in the treatment of B-cell chronic lymphocytic leukaemia (B-CLL), in patients with sufficient healthy blood cell production.

First treatment for chronic lymphocytic leukaemia with Fludarabine phosphate 25 mg/ml should only be started in patients with advanced disease having disease related symptoms or evidence of disease progression.

2 What you need to know before you are given 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 you are **breast-feeding**.
- if you have severe **kidney problems**.
- If your red blood cell count is low, because of a type of **anaemia** (decompensated haemolytic anaemia). Your doctor will have told you if you have this condition.

Tell your doctor, if you think any of these may apply to you.

Warnings and precautions
Talk to your doctor before using Fludarabine phosphate 25 mg/ml:

Take special care with Fludarabine phosphate 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 phosphate 25 mg/ml before. During treatment with Fludarabine phosphate 25 mg/ml 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 phosphate 25 mg/ml.

- **if you notice any unusual symptoms of your nervous system such as disturbed vision , headache, confusion, seizures**.
- Tell your doctor.

If Fludarabine phosphate 25 mg/ml 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.

When fludarabine is used at the recommended dose, following the treatment with some other medications or at the same time as some other medications, the following adverse events have been reported: neurological disorders manifested by headache, feeling sick (nausea) and vomiting, seizures, visual disturbances including vision loss, changes in mental status (thinking abnormal, confusion, altered consciousness) and occasionally neuromuscular disorders manifested by muscle weakness in your limbs (including irreversible partial or complete paralysis) (symptoms of *leukoencephalopathy*, *acute toxic leukoencephalopathy or posterior reversible leukoencephalopathy syndrome (RPLS)*).

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 had been stopped. In some patients receiving Fludarabine phosphate 25 mg/ml doses higher than the recommended dose, leukoencephalopathy (LE), acute toxic leukoencephalopathy (ATL) or posterior reversible leukoencephalopathy syndrome (RPLS) have also been reported. Same symptoms of LE, ATL or RPLS as above described could occur.

LE, ATL, and RPLS may be irreversible, life-threatening, or fatal.

Whenever LE, ATL or RPLS is suspected, your treatment with Fludarabine phosphate 25 mg/ml will be stopped for further investigations. If the diagnosis of LE, ATL, or RPLS is confirmed, you doctor will permanently discontinue your treatment with Fludarabine phosphate 25 mg/ml.

- **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 phosphate 25 mg/ml. 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 phosphate 25 mg/ml (or have been).**
- Tell your doctor.

- **if you need a blood transfusion and you are being treated with Fludarabine phosphate 25 mg/ml (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 during Fludarabine phosphate 25 mg/ml therapy or afterwards. You may develop skin cancer during or after Fludarabine phosphate 25 mg/ml therapy.

Other things to consider, while you are treated with Fludarabine phosphate 25 mg/ml :

- **Fludarabine phosphate 25 mg/ml must not be administered if you are pregnant unless clearly indicated by your doctor.**

Females: you must not become pregnant during treatment with Fludarabine phosphate 25 mg/ml and must use an effective method of contraception during and for 6 months after end of treatment, because this medicine may be harmful for the unborn baby. If pregnancy occurs during your treatment, you must immediately inform your doctor. Your doctor will decide with you whether you should carry on taking this medicine.

Males: you are advised not to father a child and must use effective method of contraception during and at least for 3 months after end of treatment. You should advice on conservation of sperm prior to treatment because Fludarabine Phosphate 25 mg/ml may alter male fertility.

- **You must not breast-feed** while you are treated with Fludarabine phosphate 25 mg/ml.

- **If you need a vaccination, check with your doctor**, because live vaccinations should be avoided during and after treatment with Fludarabine phosphate 25 mg/ml.

- **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 section 2 '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**, you will be monitored especially closely.

Children and adolescents
The safety and effectiveness of this medicine in children below the age of 18 years have not been established. Therefore, Fludarabine phosphate 25 mg/ml is not recommended for use in children.

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 drugs. They may reduce the effectiveness of Fludarabine phosphate 25 mg/ml.
- **cytarabine** (*Ara-C*) used to treat chronic lymphatic leukaemia. If Fludarabine phosphate 25 mg/ml is combined with cytarabine, levels of the active form of cytarabine in leukaemic cells may rise. However, the overall levels of cytarabine 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.

Pregnancy
Females: you must not become pregnant during treatment with Fludarabine phosphate 25 mg/ml because animal studies and very limited experience in humans have shown a possible risk of abnormalities in the unborn baby as well as early pregnancy loss or premature delivery. If pregnancy occurs during your treatment, you must immediately inform your doctor. Your doctor will decide with you whether you should carry on taking this medicine.

Breast-feeding
You must not breast-feed while you are treated with Fludarabine phosphate 25 mg/ml.

Fertility in males and females
Females: you must use an effective method of contraception during and for 6 months after end of treatment, because this medicine may be harmful for the unborn baby.

Males: You are advised not to father a child and must use an effective method of contraception during and at least for 3 months after end of treatment. You should seek advice on conservation of sperm prior to treatment because this medicine may alter male fertility.

Both men and women who are planning to have a child after treatment are advised to talk to a doctor before start of Fludarabine phosphate 25 mg/ml treatment.

Driving and using machines
Some people get tired, feel weak, have disturbed vision, become confused, or agitated or have seizures while they are treated with Fludarabine phosphate 25 mg/ml. Do not try to drive or operate machines until you are sure that you are not affected.

Fludarabine phosphate 25 mg/ml contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3 How to use Fludarabine phosphate 25 mg/ml

Fludarabine phosphate 25 mg/ml should be administered 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.

How much Fludarabine phosphate 25 mg/ml 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 the doctor from your height and weight.
The recommended dose is 25 mg fludarabine phosphate/m^2 body surface area.

How Fludarabine phosphate 25 mg/ml is given
Fludarabine phosphate 25 mg/ml is given 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 Fludarabine phosphate 25 mg/ml is not given beside the vein (paravenously). However, if this happens, no severe local adverse events have been reported.

For how long Fludarabine phosphate 25 mg/ml 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. In general this is after six cycles, in other words after approximately 6 months.

How long the treatment lasts depends on how successful your treatment is and how well you tolerate Fludarabine phosphate 25 mg/ml. The dosage may be decreased or the repeat course may be delayed if side effects are a problem.

You will have regular blood tests during your treatment. Your individual dose will be carefully adjusted according to the number of your blood cells and your response to the therapy.
If you have kidney problems or if you are over the age of 65, you will have regular tests to check your kidney function. If your kidneys do not work properly you may be given this medicine at a lower dose. If your kidney function is severely reduced you will not be given this medicine at all (see section 2).

If any Fludarabine phosphate 25 mg/ml solution is accidentally spilt
If any of the Fludarabine phosphate 25 mg/ml 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 Fludarabine Phosphate 25 mg/ml is given than it should
If you may have received an overdose, your doctor will stop the therapy and treat the symptoms.

High doses can lead to a severely reduced number of blood cells. For fludarabine given intravenously it has been reported that overdose can cause delayed blindness, coma, and even death.

If a dose of Fludarabine Phosphate 25 mg/ml is forgotten.
Your doctor will set the times at which you are to receive this medicine. Talk to your doctor as soon as possible, if you think you may have missed a dose.

If you stop using Fludarabine phosphate 25 mg/ml
You and your doctor may decide to stop your treatment with Fludarabine phosphate 25 mg/ml if the side effects are becoming too severe.

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 side effects below are, ask your doctor to explain them to you.
Some side effects can be life-threatening. **Tell your doctor immediately:**

- **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 (very common side effect: may affect more than 1 in 10 people).
- **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 (very common side effect: may affect more than 1 in 10 people).
- **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 'Warnings and precautions') (uncommon side effect: may affect up to 1 in 100 people).
- **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)* (rare side effect: may affect up to 1 in 1,000 people).
- **if you have palpitations (if you suddenly become aware of your heart beat) or chest pain**. These may be signs of heart problems (rare side effect: may affect up to 1 in 1,000 people).

Other possible side effects:

Very common side effects (may affect more than 1 in 10 people):
- infections (some serious);
- 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, diarrhea, feeling sick *(nausea);*
- fever;
- feeling tired *(fatigue)*;
- weakness.

Common side effects (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 side effects (may affect up to 1 in 100 people):
- autoimmune disorder (see section 2 '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 side effects (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;

Not known (frequency cannot be estimated from the available data):
- bleeding in the brain (*cerebral haemorrhage*)
- neurological disorders manifested by headache, feeling sick (nausea) and vomiting, seizures, visual disturbances including vision loss, changes in mental status (thinking abnormal, confusion, altered consciousness), and occasionally neuromuscular disorders manifested by muscle weakness in your limbs (including irreversible partial or complete paralysis) (symptoms of *leukoencephalopathy, acute toxic leukoencephalopathy* or *posterior reversible leukoencephalopathy syndrome (RPLS)*)
- bleeding in the lungs (*pulmonary haemorrhage)*
- inflammation of the bladder, which can cause pain when passing urine, and can lead to blood in the urine (*haemorrhagic cystitis*).

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
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.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation holder: TEVA UK Limited, Ridings Point, Whistler Drive, Castleford, WF10 5HX, United Kingdom.
Company responsible for manufacture: Pharmachemie B.V., 2003 RN Haarlem, the Netherlands.

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