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 or nurse.
- If you get any side effects, talk to your doctor 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 is and what it is used for

Fludarabine Phosphate is an anti-cancer drug.

Fludarabine Phosphate is used to treat chronic B-cell lymphocytic leukaemia (B-CLL) in patients with sufficient healthy blood cell production. This is a type of cancer of white blood cells (the cells are called lymphocytes).

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.

2. What you need to know before you use Fludarabine Phosphate

Do not use Fludarabine Phosphate:
- 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 your kidney function is severely impaired.
- If you have a low number 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.

Warnings and precautions
Talk to your doctor or nurse before using Fludarabine Phosphate if:

- Your liver does not work properly, as your doctor may give you this medicine with caution.

- You have any form of kidney disease, as your kidney function should be checked regularly. If it is found that your kidneys do not work properly you may be given this medicine at a reduced dose. If your kidneys work at only a very low level you will not be given this medicine at all. Patients aged 65 years or older should have their kidney function checked before start of treatment.

- You are not feeling very well, as your doctor may decide not to give you this medicine, or may give you this medicine with caution. This is very important if your bone marrow is not working properly or if you are susceptible to infections.

- You notice any unusual bruising, excessive bleeding after injury or if you seem to be catching a lot of infections. The number of normal blood cells may be reduced and so you will have regular blood tests during treatment.

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 (autoimmune disorder). It may also be directed against your red blood cells (called 'autoimmune haemolysis'). This condition can be life threatening. If this condition occurs you may receive further medication such as transfusion of blood (irradiated, see below) and corticosteroids.

If you need a blood transfusion and you are being (or have been) treated with this medicine, you should mention this to the doctor. Your doctor will ensure that you receive blood only, which has gone through a special treatment (irradiation). There have been severe complications and even death reported when non-irradiated blood has been given.

If you need to have stem cells collected and you are being (or have been) treated with this medicine, you should mention this to the doctor.

There is little information on the effects of Fludarabine Phosphate in patients aged 75 years and older. Your doctor will use it with caution if you are in this age group.

If you have very severe chronic lymphocytic leukaemia, your body may not be able to get rid of all the waste products from the cells destroyed by Fludarabine Phosphate This is called tumour lysis syndrome and may cause dehydration, kidney failure and heart problems. Your doctor will be aware of this and may give you other medicines to stop this happening.

If you experience any unusual symptoms from the nervous system you should mention it to your doctor. This is because when used in patients at doses four times greater than the recommended dose, severe central nervous system (brain and spinal cord) effects including blindness, coma and death have been reported.

Tell your doctor if you notice any changes to your skin either while you are receiving this medicine or after you have finished the course of therapy. The doctor should check the seriousness of the skin changes. If you have skin cancer, the damaged areas of your skin may become worse when you use this medicine.

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.

Check with your doctor about any vaccinations you may need, because live vaccinations should be avoided during and after treatment with Fludarabine Phosphate.

Children and adolescents
Fludarabine Phosphate is not recommended for use in children and adolescents below age 18. No data are available concerning the use of Fludarabine Phosphate in the paediatric population.

Other medicines and Fludarabine Phosphate
Tell your doctor if you are taking, have recently taken or might take any other medicines.

It is especially important to tell your doctor about:

- **Pentostatin** *(deoxycoformycin)*, which is also used to treat B-CLL. Taking these two drugs together can lead to severe lung problems (which can be life-threatening), so combination with Fludarabine Phosphate is not recommended.
- **Dipyridamole** (or other similar substances), which is used to prevent excessive blood clotting. They may reduce the effectiveness of Fludarabine Phosphate.
- **Cytarabine** (*Ara-C*), which is used to treat chronic lymphatic leukaemia. If Fludarabine Phosphate is combined with cytarabine, levels of the active form of cytarabine (*Ara-CTP*) 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 for advice before taking this medicine.

Fludarabine Phosphate treatment has the potential to harm the unborn child. You should not be given Fludarabine Phosphate if you are pregnant unless clearly necessary and when the potential benefits justify the potential risks to the unborn child. If you are a woman who may still be fertile, you must avoid becoming pregnant during treatment and for at least 6 months after stopping treatment. However, if you do become pregnant inform your doctor immediately.

Men who are treated with Fludarabine Phosphate and can father a child must use a reliable form of contraception during, and for at least 6 months after stopping treatment.

It is not known if this medicine appears in the breast milk of women treated with Fludarabine Phosphate. However, in animal studies the medicinal product was found in breast milk. Therefore you must not breast feed during your treatment with this medicine.

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. Do not try to drive or operate machines until you are sure that you are not affected.

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

3. How to use Fludarabine Phosphate

Fludarabine Phosphate should be administered under the supervision of a qualified doctor experienced in cancer therapy.

The dose you are given depends on the size of your body. It varies with your body surface area. Technically this is measured in square metres (m^2), but is actually worked out from your height and weight. The recommended dose is 25 mg/m^2 body surface. This will be given either as an injection or as an infusion (with a drip) into a vein once a day for 5 consecutive days every 28 days. This five 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 cycles). The dosage may be decreased or the repeat course delayed if side effects are a problem. 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 also section 2, 'Do not use Fludarabine Phosphate:')*.
The safety of this drug in children and adolescents below age 18 has not been established and treatment is not recommended.

If any of the Fludarabine Phosphate 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 lots of water. Try not to breathe in any fumes coming from the solution.

If you use more Fludarabine Phosphate than you should
In the case of an overdose your doctor will stop the therapy and treat the symptoms.
Symptoms of an overdose can be blindness which may not appear until later, 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 you forget to use Fludarabine Phosphate
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 product, ask your doctor 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. **You must contact your doctor immediately if you notice any of the following:**
- **Difficulty breathing, a cough, or chest pain with or without fever.** These may be signs of an infection of the lungs (*pneumonia*).
- **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.
- **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).
- **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)*.
- **You have palpitations (if you suddenly become aware of your heart beat) or chest pain.** These may be signs of heart problems.

Below we list other 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);
- 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):
- Attack of the immune system on parts of the body or red blood cells *(autoimmune disorder);*
- 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;
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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 in the brain (*cerebral haemorrhage*)
- Bleeding in the lungs (*pulmonary haemorrhage*)

Reporting of side effects
If you get any side effects, talk to your doctor 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

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

Vial before opening:
Store between 2-8°C.

After dilution:

The diluted solution of Fludarabine Phosphate in 0.9% sodium chloride is stable for up to 28 days in PVC and PE bags at 2-8°C and at 25°C when protected from light.
From a microbiological point of view, the product must 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP.

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 contains

- The active substance is fludarabine phosphate. 1 ml of concentrate contains 25 mg fludarabine phosphate. Each 2 ml vial contains 50 mg fludarabine phosphate.
- The other ingredients are disodium phosphate dihydrate, water for injections, sodium hydroxide (for pH adjustment).

What Fludarabine Phosphate looks like and contents of the pack

Fludarabine Phosphate is a clear, colourless or almost colourless solution.

Colourless glass vial (type I) with bromobutylic rubber stopper and metallic cap (aluminium) with polypropylene disk. Vial will be packed with or without a protective plastic overwrap.

Pack sizes
2 ml vial
5 x 2 ml vial

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Actavis Group PTC ehf
Reykjavikurvegi 76-78,
220 Hafnarfjordur, Iceland

Manufacturer

Actavis Italy S.p.A
Via Pasteur 10, 20014 Nerviano (Milan)
Italy

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If you would like a leaflet with larger text, please contact
UK: 01271 385257
IE: 1890 333231

<Other sources of information>

<Detailed information on this medicine is available on the website of {MS/Agency}>

<The following information is intended for healthcare professionals only:>

Fludarabine Phosphate 25 mg/ml concentrate for solution for injection/infusion

Instructions for use, handling and disposal

ANTINEOPLASTIC AGENT

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

Instructions for use

This medicinal product must not be mixed with other medicinal products, other than 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.

Inspection prior to use
Only clear, colourless to yellowish solutions without particles should be used. /.../ should not be used in case of a defective container.

Storage conditions after dilution:
The diluted solution of Fludarabine Phosphate in 0.9% sodium chloride is stable for up to 28 days in PVC and PE bags at 2-8°C and at 25°C when protected from light. From a microbiological point of view, the product must 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Handling and disposal
Fludarabine Phosphate 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 Fludarabine Phosphate solution. The use of protective 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 for cytotoxic agents.