PACKAGE LEAFLET: INFORMATION FOR THE USER

Fludarabine Phosphate 50 mg Powder 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 or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their sign of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist.This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Fludarabine Phosphate Powder for Solution for Injection or Infusion is and what it is used for

Fludarabine phosphate is an anti-cancer medicine. Fludarabine phosphate is used in the treatment of B-cell chronic lymphocytic leukaemia (B-CLL) in patients who have a sufficient amount of healthy blood cells in their bone marrow.

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.

Fludarabine phosphate works by stopping the growth of new cancer cells. 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. Fludarabine phosphate is taken up by the cancer cells and works by hindering the production of new DNA.

In cancers of the white blood cells (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. If there are too many abnormal white blood cells, they push aside healthy blood cells - which can result in infections, decrease in number of red blood cells (anaemia), bruising, unusually severe bleeding or even organ failure.

2. What you need to know before you are given Fludarabine Phosphate Powder for Solution for Injection or Infusion

Do not use Fludarabine Phosphate Powder for Solution for Injection or Infusion

- 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
- 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.
- if you are breast-feeding (see section Pregnancy and Breast-feeding)

It is important that you tell your doctor if you have problems even if those are on the above list or not.

Warnings and precautions

Talk to your doctor or pharmacist before using Fludarabine Phosphate for Solution for Injection or Infusion

– because the active substance of Fludarabine Phosphate Powder for Solution for Injection or Infusion, fludarabine phosphate, is a very ***strong active substance***.

Therefore, the side effects can be very serious and toxic (poisonous). For these reasons, your doctor will watch you closely if he/she prescribed you fludarabine phosphate. Therefore, it is very important that you report to your doctor all side effects which occur during the use of fludarabine phosphate.

This concerns mainly the following adverse events:

- You are not feeling well.
  This is especially important to report if your bone marrow is not working properly, if your immune system is not working well or if you are susceptible to infections.
- After injury you notice unusual bruising or excessive bleeding.
  This can point to a reduction in healthy blood cells.
- Changes of your skin, such as rash or blisters.
  This is especially important if you have or have had skin cancer.

Your doctor may decide not to give you fludarabine phosphate, or to give you this medicine with special precautions, if you experience one of the above mentioned side effects.

You will have regular blood checks during treatment

- if you are catching a lot of infections (if you have a poorly functioning or depressed immune system or a history of serious infections).

Your immune system may attack different parts of your body (called 'autoimmune phenomenon'), and this may also be directed against your red blood cells (called 'autoimmune haemolysis'). This condition can be life threatening and even lead to death. If you experience this condition you may receive further medication such as transfusion of blood (irradiated, see below) and adrenocorticoids.

– when you receive a ***high dose***. When fludarabine phosphate is used in patients with acute leukaemia at very high doses (up to four times greater than the recommended dose for CLL) a third of patients experienced severe central nervous system effects (including blindness, coma and death). In patients receiving the recommended dose for CLL, coma, seizures or agitation are rare events. Confusion occasionally occurs. You should mention to your doctor any unusual symptoms you experience. Some of these symptoms appeared delayed around 60 days or more after treatment has been stopped.

– when you use fludarabine for a ***lengthy period***. The effect of long-term use of fludarabine phosphate on the central nervous system is unknown. However, some people have endured the recommended dose for up to 26 courses of therapy.

– if you need a ***blood transfusion*** and you are being (or have been) treated with fludarabine phosphate, you should mention this to your 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 fludarabine phosphate, tell your doctor that you have received fludarabine phosphate.

– when you need a ***vaccination***; consult your doctor, because live virus vaccines should be avoided during and after treatment with fludarabine phosphate.

– 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 may cause dehydration, reduced kidney function and heart problems from the first week of treatment and is called tumour lysis syndrome. Your doctor will be aware of this and may give you other drugs to deal with this problem.

– if you have ***skin cancer***, the damaged areas of your skin may become worse when you use this medicine. You may develop skin cancer during or after treatment with fludarabine phosphate. Tell your doctor if you notice any changes to your skin either while you are receiving this medicine or even after you have finished taking this medicine.

– with ***children***. The safety and effectiveness of fludarabine phosphate has not been established. Therefore, fludarabine phosphate is not recommended for use in children.

– with ***men and women who may still be fertile***; see Section “Pregnancy and breast-feeding”.

– if your ***liver*** does not work properly; your doctor may decide not to give you this medicine, or may give you this medicine with caution.

– if you have any form of ***kidney*** disease or if you are ***over 65 years*** old, your kidney function should be checked regularly. If your kidneys are found not to work properly you may be given fludarabine phosphate at a reduced dose. If your kidneys work at only a very low level you will not be given this medicine at all.

– if you are ***over 75 years*** old, fludarabine phosphate will be given with caution.

Consult your doctor if one of the above mentioned warnings is applicable to you, or has been in the past.

Other medicines and Fludarabine Phosphate

Attention: the following remarks can also apply to the use of medicines in the past or in the near future.

The medicines mentioned in this section may be known to you under a different name, often the brand name. In this section only the name of the active ingredient or group of active ingredients of the medicine is mentioned and not the brand name! Therefore, check on the package or insert what the active ingredient is of the medicine you are using.

An interaction means that medicines, when used at the same time, can influence each other’s action and/or side effects. An interaction can occur with this medicine when used together with:

- ***pentostatin*** (=deoxycoformycin) (another medicine that inhibits the growth of cancer); you may not be treated with fludarabine phosphate
- ***some blood thinning medicines***, such as ***dipyridamole***; they 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 fludarabine phosphate in the cell may rise. However, the overall

levels in the blood and its elimination from the blood were not shown to have changed

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

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 doctore or pharmacist for advice before taking this medicine, because animal studies and limited experience in humans have shown a possible risk of abnormalities in the developing foetus. Your doctor will carefully weigh up the benefit of your treatment against a possible risk for an unborn child and, if you are pregnant, will only prescribe fludarabine phosphate if clearly necessary.

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.

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.

Ask your doctor for advice before taking any medicine.

Driving and using machines

Some people get tired, feel weak, have disturbed vision, become confused or agitated or have seizures while they are being treated with fludarabine phosphate. Do not try to drive or operate machines until you are sure that you are not affected.

Important information about some of the ingredients of Fludarabine Phosphate Powder for Solution for Injection or Infusion

Fludarabine Phosphate Powder for Solution for Injection or Infusion contains less than 1 mmol sodium (23 mg) per 1 ml (when the contents of the vial is dissolved in 2 ml of water), *i.e.* essentially ‘sodium-free’.

3. How to use Fludarabine Phosphate Powder for Solution for Injection or Infusion

Fludarabine phosphate should be used under the supervision of a qualified doctor experienced in the use of anticancer therapy.

Always take this medicine exacty as described in this leaflet or as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will decide when and how long fludarabine phosphate will be given to you. *Consult your doctor if you have the feeling that fludarabine phosphate is acting too strongly or not strongly enough.*

The administered amount of fludarabine phosphate (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.

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 are over the age of 70, 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 you take more Fludarabine Phosphate Powder for Solution for Injection or Infusion than you should

As this medicine is given in a hospital, it is unlikely that you will be given too little or too much, however tell your doctor if you have any concerns.

There is no specific antidote for fludarabine phosphate overdosage. If you received too much fludarabine phosphate the doctor will stop the therapy and treat the symptoms.

High doses of fludarabine phosphate 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 you forget to take Fludarabine Phosphate Powder for Solution for Injection or Infusion.

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.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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 people *(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 a condition called *tumour lysis syndrome*.

- If you notice any blistering of the skin, mouth, eyes and genitals, inflammation, blistering and tissue break down. These may be signs of a severe reaction (*Lyell's syndrome, Stevens-Johnson syndrome)*.

- If you have palpitations (awareness 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.

If you are not sure what the side-effects listed below are, ask your doctor to explain them to you.

Very common: affects more than 1 user in 10
- 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: affects 1 to 10 users in 100
- 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: affects 1 to 10 users in 1,000
- autoimmune disorder;
- tumour lysis syndrome;
- 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: affects 1 to 10 users in 10,000
- 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
- cerebral haemorrhage *(bleeding in the brain);*
- pulmonary haemorrhage *(bleeding in the lungs);*
- 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 or pharmacist. This includes any possible side effects not listed in this leaflet.

You can also report side effects directly via:

Ireland
HPRA Pharmacovigilence
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 Powder for Injection or Infusion

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

As packaged for sale: Do not store above25°C.
For storage conditions after reconstitution and dilution: please refer to section 'Information for medical and healthcare professionals'

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.

Any vials which are damaged in anyway should be discarded.

The reconstituted solution is clear and colourless. Do not use this medicine if you notice that the solution is not clear, colourless and particle free..

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 to protect the environment.

6. Contents of the pack and other information

What Fludarabine Phosphate Powder for Solution for Injection or Infusion contains

- The active substance is fludarabine phosphate. Each vial contains 50 mg fludarabine phosphate

- The other ingredients are mannitol and sodium hydroxide used as a pH adjuster

1 ml of reconstituted solution contains 25 mg of fludarabine phosphate.

What Fludarabine Phosphate Powder for Solution for Injection or Infusion looks like and contents of the pack

Fludarabine Phosphate Powder for Solution for Injection or Infusion is a sterile white to off-white powder for solution for injection or infusion in a 10 ml clear, colourless vial sealed with a rubber closure and a flip-off cap. The powder is reconstituted with Water for Injection and further diluted.

The reconstituted solution is clear and colourless.

Fludarabine Phosphate Powder for Solution for Injection or Infusion is available in packs containing 5 vials.

Marketing Authorisation Holder and Manufacturer

Hospira UK Limited
Queensway
Royal Leamington Spa
Warwickshire
CV31 3RW
UK

For any information about this medicinal product, please contact the Marketing Authorisation Holder detailed above.

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

Denmark:	Fludarabinphosphat Hospira 50 mg pulver til injektions- og infusionsvæske, opløsning
Finland:	Fludarabin Hospira 50 mg injektio-/infuusiokuiva-aine, liuosta varten
France:	FLUDARABINE PHOSPHATE HOSPIRA 50mg, poudre pour solution injectable ou perfusion
Ireland:	Fludarabine Phosphate 50 mg Powder for Solution for Injection or Infusion
Italy:	Fludarabina Fosfato Hospira 50 mg Polvere per Soluzione per Iniezione o Infusione
Norway:	Fludarabinphosphat Hospira 50 mg pulver til injeksjons-/ infusjonsvæske, oppløsning
Portugal:	Fludarabina Hospira 50 mg pó para solução injectável MG
Spain:	Fosfato de fludarabina Hospira 50 mg polvo para solución inyectable o para perfusión
Sweden:	Fludarabinphosphat Hospira 50mg pulver till injektions-/infusionsvätska, lösning

UK: Fludarabine Phosphate 50 mg Powder for Solution for Injection or Infusion

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The following information is intended for healthcare professionals only:

Fludarabine Phosphate Powder for Solution for Injection or Infusion as other potiential cytotoxic medicines should be prepared by qualified personnel in a designated area. Consideration should be given to handling and disposal according to guidelines used for cytotoxic drugs.

For intravenous use only

Incompatibilities
Must not be mixed with other drugs.

Instructions for use and handling

Reconstitution
Fludarabine Phosphate Powder for Solution for Injection or Infusion should be prepared for use by aseptically adding sterile Water for Injections.
When reconstituted with 2 ml of sterile Water for Injections, the powder should fully dissolve in 15 seconds or less. Each ml of the resulting solution will contain 25 mg of fludarabine phosphate. The solution should be inspected visually. The reconstituted solution should be clear, colorless and without particles.

Dilution
The reconstituted solution draws up into a syringe. For intravenous bolus injection this dose is further diluted into 10 ml 0.9 % sodium chloride. For intravenous infusion the solution is diluted into 100 ml 0.9 % sodium chloride and infused over 30 minutes. In clinical studies, the product has been diluted in 100 ml or 125 ml of 5 % dextrose (for injection) or 0.9 % sodium chloride solution.

Storage
Shelf-life after reconstitution: After reconstitution with sterile Water for Injections to concentration of 25 mg/ml, should the product be stored in 2°C-8ºC protected against light or in 25°C in normal light up to 8 hours. Reconstituted solution with sodium chloride 0.9 % or glucose 5 % is chemically stable stored in infusion bag in 2°C-8ºC protected against light or in 25°C in normal light up to 8 hours.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. In-use storage times and

conditions prior to use and would normally not be longer than 8 hours at 2-8°C or 8 hours at room temperature.

If any fludarabine phosphate solution is accidentally spilt:
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 plenty of tap water. Avoid any exposure by inhalation.