Package leaflet: Information for the user
Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion
Fludarabine phosphate

The name of your medicine is Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion. In the rest of this leaflet your medicine is called Fludarabine phosphate Injection.

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 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, or 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 Injection is and what it is used for
2. What you need to know before you use Fludarabine phosphate Injection
3. How to use Fludarabine phosphate Injection
4. Possible side effects
5. How to store Fludarabine phosphate Injection
6. Contents of the pack and other information

1. What Fludarabine phosphate Injection is and what it is used for

Fludarabine phosphate Injection 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 Injection 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 Injection 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 this medicine 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 Injection

Do not use Fludarabine phosphate Injection :

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

Warnings and precautions

Talk to your doctor before using Fludarabine phosphate Injection:

- **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**.

- **If during treatment you have a red to brownish urine, or have a rash or any blisters on your skin.**

  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 this medicine before. During treatment with Fludarabine phosphate Injection 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 this medicine.

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

  If Fludarabine phosphate Injection 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 phosphate Injection 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 Injection 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 Injection 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 Injection.

- **If you notice any pain in your side, blood in your urine or reduced amount of urine,**

  When your disease is very severe, your body may not be able to clear all the waste products from the cells destroyed by this medicine. 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 Injection (or have been),**

- **If you need a blood transfusion and you are being treated with Fludarabine phosphate Injection (or have been),**

  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,**

- **If you have or have had skin cancer** it may worsen or flare up again during Fludarabine phosphate Injection therapy or afterwards. You may develop skin cancer during or after Fludarabine phosphate Injection therapy.

Other things to consider, while you are treated with Fludarabine phosphate Injection :

- **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 phosphate Injection 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 phosphate Injection if clearly necessary.

- **If you consider or are breastfeeding** you should not start it or continue while on treatment with Fludarabine phosphate Injection .

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

- **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 section 2 and 3)*.

Children and adolescents

The safety and effectiveness of Fludarabine phosphate Injection in children below the age of 18 years has not been established. Therefore, this medicine is not recommended for use in children.

Older patients and Fludarabine phosphate Injection:
People over 65, will have regular tests for kidney function (see also section 3. How to use Fludarabine phosphate Injection).
People over 75, will be monitored especially closely.

Other medicines and Fludarabine phosphate Injection:

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

- **cytarabine** (*Ara-C*) used to treat chronic lymphatic leukaemia. If Fludarabine phosphate Injection is combined with cytarabine, levels of the active form of Fludarabine phosphate Injection 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 and breast-feeding and fertility:

Pregnancy
Fludarabine phosphate Injection should not be given to women who are pregnant 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 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.

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 prescribe this medicine if clearly necessary.

Breast-feeding:
You must not start or continue breast feeding during your treatment with this medicine, as this medicine may interfere with the growth and development of your baby.

Fertility
Men and women, who are fertile, must use effective contraception during treatment and for at least 6 months afterwards.

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 this medicine. 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 Injection
This medicinal product contains less than 1mmol sodium per dose, i.e, essentially sodium free.

3. How to use Fludarabine phosphate Injection

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Fludarabine phosphate Injection should be administered under the supervision of a qualified doctor experienced in the use of anti-cancer therapy.

- For information for preparation of the diluted solution, see section 6. Contents of the pack and other information.

How much Fludarabine phosphate Injection 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 your doctor from your height and weight.

The recommended dose is 25 mg fludarabine phosphate/m^2 body surface area.

How Fludarabine phosphate Injection is given:

Fludarabine phosphate Injection is given in the form of a solution 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 Injection is not given beside the vein (paravenously). However, if this happens, no severe local adverse events have been reported.

For how long Fludarabine phosphate Injection 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 (usually after 6 courses).

How long the treatment lasts depends on how successful your treatment is and how well you tolerate this medicine. 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.

The dosage may be decreased 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)*.

If any Fludarabine phosphate Injection solution is accidentally spilt:

If any of the Fludarabine phosphate Injection 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 Injection 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 phosphate Injection given intravenously it has been reported, that overdose can cause delayed blindness, coma and even death.

If a dose of Fludarabine phosphate Injection 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.

Do not take a double dose to make up for a forgotten dose.

If the treatment with Fludarabine phosphate Injection is stopped:
You and your doctor may decide to stop your treatment with this medicine if the side effects are becoming too severe.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

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).
- **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 (less than 1 in every 1000 patients) 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, diarrhea, 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'Warnings and precautions').
  - Tumour lysis syndrome (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** (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 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
  - Bleeding in the lungs.
  - 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)).

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

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

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

- *Storage of Fludarabine phosphate Injection as packed for sale*

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

- *Storage of Fludarabine phosphate Injection after dilution*

Chemical and physical in-use stability has been demonstrated at 0.2 mg/ml and 6.0 mg/ml after dilution with 0.9% Sodium chloride and 5% Glucose Injection for 7 days at 2-8 °C and 5 days at 20 – 25 °C in non-PVC bags and Glass bottles.

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 should not be longer than 24 hours at 2 to 8 °C unless dilution has taken place in controlled and validated aseptic conditions.

For information for medical and healthcare professionals, see section 6. Contents of the pack and other information.

Do not use this medicine if you notice any visible signs of deterioration.

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 Injection contains:

- **The active substance is** fludarabine phosphate. Each ml contains 25 mg fludarabine phosphate.
- **The other ingredients are** mannitol, disodium hydrogen phosphate dihydrate and water for injection

Fludarabine phosphate Injection is provided in 2-ml glass vials.

What Fludarabine phosphate Injection looks like and contents of the pack:
Fludarabine phosphate Injection is a sterile, clear, colourless or slightly brownish-yellow solution in a clear glass vial.

Fludarabine phosphate Injection is available in three pack sizes, containing either 1 vial, 5 vials or 10 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:
Marketing Authorisation Holder
Accord Healthcare Limited,
Sage House,
319 Pinner Road,
North Harrow,
Middlesex, HA1 4HF,
United Kingdom

Manufacturer

Accord Healthcare Polska Sp.z o.o.,
ul. Lutomierska 50,95-200 Pabianice, Poland

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

Country	**Proposed Name**
Austria	Fludarabine Accord 25 mg/ml Konzentrat zur Herstellung einer Injektions-oder Infusionslösung
Belgium	Fludarabine Accord Healthcare 25 mg/ml Concentraat voor oplossing voor injectie of infusie
Bulgaria	Fludarabine Accord 25 mg/ml Concentrate for Solution for Injection or Infusion
Cyprus	Fludarabine Accord 25 mg/ml, Concentrate for Solution for Injection or Infusion
Germany	Fludarabin Accord 25 mg/ml Konzentrat zur Herstellung einer Injektions-oder Infusionslösung

Estonia	Fludarabine Accord 25 mg/ml
Spain	Fludarabina Accord 25 mg/ml Concentrado para solución inyectable o para perfusión
Finland	Fludarabine Accord 25 mg/ml Liuosta varten injektiona tai infuusiona
France	Fludarabine Accord 25 mg/ml, Concentré pour solution injectable ou pour perfusion
Hungary	Fludarabin Accord 25 mg/ml koncentrátum oldatos injekcióhoz vagy infúzióhoz
Ireland	Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion
Italy	Fludarabina Accord
Latvia	Fludarabine Accord 25 mg/ml koncentrāts injekciju vai infūziju šķīduma pagatavošanai
Lithuania	Fludarabine Accord 25 mg/ml koncentratas injekciniam/infuziniam tirpalui
Malta	Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion
Netherlands	Fludarabine Accord 25 mg/ml, Concentraat voor oplossing voor injectie of infusie
Portugal	Fludarabina Accord
Sweden	Fludarabine Accord
United Kingdom	Fludarabine phosphate 25 mg/ml Concentrate for Solution for Injection or Infusion

This leaflet was last revised in 06/2022

The following information is intended for medical or healthcare professionals only:

Fludarabine phosphate Injection as other potential 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
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

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 sodium chloride 9mg/ml (0.9%). Alternatively, for infusion, the required dose may be diluted in 100 ml sodium chloride 9mg/ml (0.9%) and infused over approximately 30 minutes.

In clinical studies, the product has been diluted in 100 ml or 125 ml of 5 % dextrose injection or sodium chloride 9mg/ml (0.9%).

Storage

As packaged for sale: 2 years.

Chemical and physical in-use stability has been demonstrated at 0.2 mg/ml and 6.0 mg/ml after dilution with 0.9% Sodium chloride and 5% Glucose Injection for 7 days at 2-8 °C and 5 days at 20 – 25 °C in non-PVC bags and Glass bottles.

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 should not be longer than 24 hours at 2 to 8 °C unless dilution has taken place in controlled and validated aseptic conditions.

Inspection prior to use
The diluted solution is clear, colourless or slightly brownish yellow solution. It should be visually inspected before use.

Only clear, colourless or slightly brownish yellow solutions without particles should be used. Fludarabine phosphate Injection should not be used in case of a defective container.

Handling and disposal
Fludarabine phosphate Injection 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 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 product, spillage or waste material should be disposed of in accordance with local requirements.