Package leaflet: Information for the user

Fludarabine phosphate 50 mg

powder 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.

What is in this leaflet:

1. What Fludarabine is and what it is used for

The name of your medicine is 'Fludarabine phosphate 50 mg powder for solution for injection/infusion' but in the rest of the leaflet it will be called 'Fludarabine'. It contains the active ingredient fludarabine phosphate. This medicine is an anti-cancer medicine that inhibits the growth of cancer cells. It is used in the treatment of B-cell chronic lymphocytic leukaemia (B-CLL), a cancer of the lymphocytes (white blood cells), in patients who have a sufficient amount of healthy blood cells in their bone marrow.

First treatment for chronic lymphocytic leukaemia with fludarabine should only be started in patients with advanced disease having disease related symptoms or evidence of disease progression.

This medicine works by stopping the growth of new cancer cells.

2. What you need to know before you use Fludarabine

Do not use Fludarabine

- if you are allergic to fludarabine 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 may or may not be used.
- 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, breast-feeding and fertility)

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 nurse before using Fludarabine.

- because the active substance of Fludarabine, 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. It is very important that you report to your doctor all side effects which occur during the use of Fludarabine.

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, 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 hemolysis'). 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 is used in patients with acute leukaemia at very high doses (up to four times greater than the recommended dose for B-CLL) a third of patients experienced severe central nervous system effects (including blindness, coma and death). In patients receiving the recommended dose for B- CLL, coma, seizures or agitation are rare events. Confusion occasionally occurs. You must 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 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, you must mention this to your doctor. Your doctor will ensure that you receive only blood, 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, tell your doctor that you have received this medicine.
- when you need a **vaccination**; consult your doctor, because live virus vaccines must be avoided during and after treatment with Fludarabine.
- 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. This may cause dehydration, reduced kidney function and heart problems. Your doctor will be aware of this and may give you other medicine to deal with this problem.
- if you have **skin cancer**, the damaged areas of your skin may become worse when you use this medicine. 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 **men and women who may still be fertile**; see Section "Pregnancy, breast-feeding and fertility".
- 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 70 years** old, your kidney function must be checked regularly. If you are aged 65 years or older your kidney function should be measured before treatment is started. If your kidneys are found not to work properly you may be given Fludarabine 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 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.

Children and adolescents

- No data are available concerning the use of Fludarabine in children and adolescents.

Other medicines and Fludarabine

Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines.

Attention: the following remarks can also apply to medicines you used in the past or may use 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** - you should not take Fludarabine with **pentostatin** because of a risk of lung damage
- **some blood thinning medicines**, such as **dipyridamole**; they reduce the effectiveness of Fludarabine
- **cytarabine** (Ara-C) which is used to treat chronic lymphatic leukaemia. If Fludarabine is combined with cytarabine, levels of the active form of fludarabine in the cell 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

Pregnancy

You should not be given Fludarabine if you are pregnant, because animal studies and limited experience in humans have shown a possible risk of abnormalities in the developing foetus. Your doctor will carefully weigh the benefit of your treatment against a possible risk for the unborn child.If you are pregnant, you will only be prescribed Fludarabine if clearly necessary.

Breast-feeding

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 must not breast feed during your treatment with this medicine.

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 taking this medicine

Fertility

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.

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

Fludarabine contains sodium

Each vial of Fludarabine phosphate 50 mg powder for solution for injection/infusion contains less than 1 mmol sodium (23 mg), i.e. essentially 'sodium-free'.

3. How to take Fludarabine

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

Carefully follow the advice of your doctor when using Fludarabine. Your doctor will decide when and how long this medicine will be given to you.

Consult your doctor if you have the feeling that fludarabine is acting too strongly or not strongly enough.

The administered amount of Fludarabine (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.

This medicine is given into a vein and the infusion lasts around 30 minutes.

General guidance

The usual 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 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 over dosage. If you received too much Fludarabine the doctor will stop the therapy and treat the symptoms.

High doses of fludarabine 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)

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The following information is intended for healthcare professionals only:
Fludarabine as other potential cytotoxic medicines must be prepared by qualified personnel in a designated area. Consideration must 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 must be prepared for use by aseptically adding sterile water for injections. When reconstituted with 2 ml of sterile water for injections, the powder must fully dissolve in less than 60 seconds. Each ml of the resulting solution will contain 25 mg of fludarabine phosphate. The solution should be inspected visually. The reconstituted/ diluted solution must 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 or 5% dextrose injection 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. The dilution compatibility study has been carried out in polyolefin infusion bags. After first opening, the product should be used immediately.

After reconstitution:
The physicochemical stability of the drug product after reconstitution in water for injections has been demonstrated for 24 hours at 25°C ± 2°C/ 60% ± 5%RH and for 7 days at 5°C ± 3°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and

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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 use Fludarabine

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 or pharmacist..

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* (a group of complications caused by the break-down products of dying cancer cells and include high levels of potassium, phosphate and uric acid as well as low levels of calcium in the blood, and the presence of excessive amounts of uric acid in the urine ***(Uncommon)***. It may possibly lead to acute uric acid nephropathy and kidney failure). If you notice any pain in your side, decreased urination or blood in your urine, tell your doctor immediately.
- **If you notice any blistering of the skin, mouth, eyes and genitals, inflammation, blistering and tissue break down.** Skin rashes are often accompanied by flu-like symptoms. These may be signs of a severe reaction (*Lyell's syndrome, Stevens-Johnson syndrome-**Rare)***.
- **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.

Below is a list of possible side effects organized by how common they are.

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 (including a condition in which the immune system attacks the red blood cells [autoimmune hemolytic anemia], immune-mediated hemolytic anemia concurrent with immune-mediated thrombocytopenia [Evans syndrome], haemorrhages in the skin, mucous membranes, and elsewhere associated with a marked reduction in the numbers of blood platelets [thrombocytopenic purpura], a bleeding disorder characterized by autoantibodies directed against a coagulation factor [acquired haemophilia], and immune-mediated skin diseases characterized by groups of itching blisters [pemphigus])
- 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*).

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet.

For UK - Also you can help to make sure that medicines remain as safe as possible by reporting any unwanted side effects via the internet at www.mhra.gov.uk/ yellowcard. Alternatively you can call Freephone 0808 100 3352 (available from 10 a.m. to 2 p.m. Mondays to Fridays) or fill in a paper form available from your local pharmacy.

5. How to store Fludarabine

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 label and carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C to 8°C).

For storage conditions after reconstitution and dilution: please refer to section 'Information for healthcare professionals'

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

The reconstituted/diluted solution is clear and colourless, only clear, colourless and particle free solutions must be used.

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 contains

- The active substance is fludarabine phosphate. Each vial contains 50 mg fludarabine phosphate. 1 ml of reconstituted solutions contains 25 mg of fludarabine phosphate.
- The other excipients are mannitol (E421) and sodium hydroxide used as a pH adjuster.

What Fludarabine looks like and contents of the pack

Fludarabine is a sterile lyophilized white or almost white powder or cake. The product is packed in type-I, 6 ml, clear, glass vials, closed with a 20 mm grey bromobutyl rubber stoppers and sealed with 20 mm green aluminum flip-off overseals. The powder is reconstituted with water for injection and further diluted.

The reconstituted/ diluted solution is clear and colourless.

Fludarabine is available in packs containing 1 vial.

Marketing Authorisation Holder and Manufacturer

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road, Bordon
Hampshire, GU35 0NF
United Kingdom

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

Bulgaria	Флударабин Каби 50 mg прах за инжекционен/инфузионен разтвор
Belgium	Fludarabine Fresenius Kabi 50 mg poeder voor oplossing voor injectie of infusie
Czech Republic	Fludarabine Kabi 50 mg prášek pro injekční/infuzní roztok
Cyprus	Fludarabine Kabi 50mg κόνις για διάλυμα προς ένεση ή έγχυση
Denmark	Fludarabin Fresenius Kabi
Estonia	Fludarabine Kabi 50 mg
France	FLUDARABINE KABI 50 mg, poudre pour solution injectable ou pour perfusion
Germany	Fludarabin Kabi 50 mg Pulver zur Herstellung einer Injektions- oder Infusionslösung
Greece	Fludarabine Kabi 50mg κόνις για διάλυμα προς ένεση ή έγχυση
Hungary	Fludarabin Kabi 50 mg por oldatos injekcióhoz vagy infúzióhoz
Ireland	Fludarabine phosphate 50 mg powder for solution for injection/ infusion
Italy	Fludarabina Kabi
Luxemburg	Fludarabin Kabi 50 mg Pulver zur Herstellung einer Injektions- oder Infusionslösung
Lithuania	Fludarabine Kabi 50 mg milteliai injekciniam/ infuziniam tirpalui
Latvia	Fludarabine Kabi 50 mg pulveris injekciju vai infūziju šķīduma pagatavošanai
Malta	Fludarabine phosphate 50 mg powder for solution for injection/ infusion
Norway	Fludarabin Fresenius Kabi
Netherland	Fludarabine Fresenius Kabi 50 mg poeder voor oplossing voor injectie of infusie
Poland	Fludarabine Kabi
Portugal	Fludarabina Kabi.
Romania	Fludarabina Kabi 50 mg pulbere pentru solutie injectabila / perfuzabila
Sweden	Fludarabin Fresenius Kabi
Slovakia	Fludarabine Kabi 50 mg prášok na injekčný a infúzny roztok
United Kingdom	Fludarabine phosphate 50 mg powder for solution for injection/ infusion

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conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2ºC to 8ºC.

After dilution:
The infusion solution is chemically stable when stored in infusion bags of 0.9 % sodium chloride solution or 5 % dextrose solution, for 48 hours when stored at 2ºC to 8ºC or 24 hours at 25ºC under normal light conditions.
From a microbiological point of view however, 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 2ºC to 8ºC, unless dilution has taken place in a controlled and validated aseptic condition.

If any fludarabine solution is accidentally spilt:
If any of the fludarabine 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.

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