Package leaflet: information for the user

Fludara® 50 mg
powder for solution for injection or infusion

Fludarabine phosphate

genzyme

Read all of this leaflet carefully before this medicine is given to you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Fludara is and what it is used for

What Fludara is and how it works:
Fludara is an intravenous injection or infusion that stops the growth of new cancer cells. All cells of the body produce new cells like themselves by dividing. Fludara 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.

What Fludara is used for:
Fludara 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 Fludara should only be started in patients with advanced disease having disease-related symptoms or evidence of disease progression.

2. Before you are given Fludara

Do not use Fludara:
- **if you are allergic** (hypersensitive) to fludarabine phosphate or any of the other ingredients of Fludara (*see section 6 Further information*)
- **if you are breast-feeding**
- **if you have severe kidney problems**
- **if your red blood cell count is low,** because of a type of anaemia (*decompensated haemolytic anaemia*) Your doctor will have told you if you have this condition.

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

Take special care with Fludara:
- If your **bone marrow** is not working properly or if you have a poorly functioning or depressed **immune system** or a history of **serious infections**

  ▷ Your doctor may decide to not give you this medicine, or may take precautions.
- **If you feel very unwell, notice any unusual bruising, more bleeding than usual after injury, or if you seem to be catching a lot of infections**

  ▷ Tell your doctor if any of these apply before your treatment.
- **If during treatment you have a red to brownish urine, or have a rash or any blisters on your skin.**

  ▷ Tell your doctor immediately.

These may be signs of a reduction in the number of blood cells, which may be caused either by the disease itself or the therapy. It can last for up to a year, independent of whether or not you had treatment with Fludara before. During treatment with Fludara 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 Fludara.
- **If you notice any unusual symptoms of your nervous system such as disturbed vision,**

  ▷ Tell your doctor.

If Fludara 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. 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 has been stopped.
- **If you notice any pain in your side, blood in your urine or reduced amount of urine,**

  ▷ Tell your doctor immediately.

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

  ▷ Tell your doctor.
- **If you need a blood transfusion and you are being treated with Fludara (or have been),**

  ▷ Tell your doctor.

In case you need a blood transfusion your doctor will ensure that you only receive blood that has been treated by irradiation. There have been severe complications and even death, from transfusions of non-irradiated blood.
- **If you notice any changes to your skin either while you are receiving this medicine or after you have finished the therapy,**

  ▷ Tell your doctor.

  If you have or have had skin cancer it may worsen or flare up again during Fludara therapy or afterwards. You may develop skin cancer during or after Fludara therapy.

Other things to consider, while you are treated with Fludara:
- **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 Fludara 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 Fludara if clearly necessary.
- **If you consider or are breast-feeding** you should not start it or continue while on treatment with Fludara.
- **If you need a vaccination, check with your doctor**, because live vaccinations should be avoided during and after treatment with Fludara.
- **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, 'Do not use Fludara' and section 3 How to use Fludara*).

Using other medicines:
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Ask your doctor or pharmacist for advice before taking any medicine.

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 substances. They may reduce the effectiveness of Fludara
- **cytarabine** (*Ara-C*) used to treat chronic lymphatic leukaemia. If Fludara is combined with cytarabine, levels of the active form of Fludara in leukaemic cells may rise. However, the overall levels in the blood and its elimination from the blood were not shown to have changed.

Older patients and Fludara:
People over 65, will have regular tests for kidney function (*see also section 3 How to use Fludara*).

People over 75, will be monitored especially closely.

Children:
The safety and effectiveness of Fludara in children has not been established. Therefore, Fludara is not recommended for use in children.

Pregnancy and breast-feeding:
Fludara 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 you think you may be pregnant,** tell your doctor immediately.
- **If you are a woman who could become pregnant,** you must use effective contraceptive methods during treatment and for at least 6 months after treatment (see section 2 'Before you are given Fludara').
- **Men who have been given Fludara** and who could become fathers must use reliable contraception during treatment and for at least 6 months afterwards.

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 Fludara if clearly necessary.

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

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 treated with Fludara. 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 Fludara
This medicinal product contains less than 1mmol sodium per dose, i.e, essentially sodium free.

3. How to use Fludara

Fludara should be administered under the supervision of a qualified doctor experienced in the use of anti-cancer therapy.
- For information for preparation of the reconstituted or diluted solution, see section 6 Further information / information for medical or healthcare professionals.

How Fludara is given:
Fludara 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 Fludara is not given beside the vein (paravenously). However, if this happens, no severe local adverse events have been reported.

How much Fludara 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.

For how long Fludara 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 Fludara. The repeat course may be delayed if side effects are a problem.

Children: Fludara is not recommended for use in children.

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, 'Do not use Fludara'*).

If any Fludara solution is accidentally spilt:
If any of the Fludara 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 Fludara 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 Fludara given intravenously it has been reported, that overdose can cause delayed blindness, coma and even death.

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

If the treatment with Fludara is stopped:
You and your doctor may decide to stop your treatment with Fludara 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, Fludara 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 2 'Take special care').
- **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 1,000 patients) were mainly identified from post-marketing experience.

- **Very common** means 1 or more in every 10 patients are likely to get these:
  - 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** means between 1 and 10 in every 100 patients are likely to get these:
  - 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** means between 1 and 10 in every 1,000 patients are likely to get these:
  - autoimmune disorder (see section 2, 'Take special care').
  - tumour lysis syndrome (see section 2, 'Take special care');
  - 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** means less than 10 in every 10,000 patients are likely to get these.
  - 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*);
- **Frequencies not known**
  - 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

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Fludara

Keep out of the reach and sight of children.

Do not use Fludara after the expiry date which is shown on the carton and vial.

The expiry date refers to the last day of that month.

- *Storage of Fludara as packed for sale*

This medicinal product does not require any special storage conditions.

- *Storage of Fludara after reconstitution*

For information for medical and healthcare professionals, see section 6 Further information, information for medicinal and healthcare professionals.

6. Further information

What Fludara contains:
- **The active substance is** fludarabine phosphate.
- **The other ingredients are** mannitol and sodium hydroxide.

The powder of Fludara is provided in 10-ml glass vials. Each vial contains 50 mg fludarabine phosphate. 1 millilitre of reconstituted solution contains 25 mg fludarabine phosphate.

What Fludara looks like and contents of the pack:
Fludara is a sterile white to off-white powder for solution for injection or infusion. The powder is reconstituted with water for injection and further diluted. The reconstituted solution is clear and colourless.

Fludara is available in packs containing 5 vials.

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This medicinal product is authorised in the Member States of the EEA under the following names:
Belgium: Fludara
France: Fludara
Germany: Fludara
Greece: Fludara
Ireland: Fludara
Italy: Fludara
The Netherlands: Fludara
Portugal: Fludara
Spain: Beneflur
UK: Fludara