**Package leaflet: Information for the user**

# Fludara® 50 mg

**powder for solution for injection or infusion**

Fludarabine phosphate

genzyme
A SANOFI COMPANY

**Read all of this leaflet carefully before you start taking 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.
- 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 Fludara is and what it is used for

Fludara 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. 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.

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. What you need to know before you are given Fludara

**Do not use Fludara:**

- 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

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

**Warnings and precautions**

Talk to your doctor before using Fludara.

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

  Tell your doctor immediatelyThese 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, headache, confusion, seizures.**

  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. When Fludara 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 Fludara doses higher than the recommended dose, leukoencephalopathy (LE), acute toxic leukoencephalopathy (ATL) or posterior reversible leukoencephalopathy syndrome (RPLS) have also been reported. Some 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 will Fludara will be stopped for further investigations. If the diagnosis of LE, ATL, or RPLS is confirmed, your doctor will permanently discontinue your treatment with Fludara.
- **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 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).**
- **if you need a blood transfusion and you are being treated with Fludara (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 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 breastfeeding** 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 sections 2 and 3).

**Children and adolescents**

The safety and effectiveness of Fludara in children below the age of 18 years has not been established. Therefore, Fludara is not recommended for use in children.

**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.

**Other medicines and Fludara**

Tell your doctor if you are taking, 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 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.

**Pregnancy, breast-feeding and fertility**

Pregnancy

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. 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.

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

**Fludara contains sodium** This medicine 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.

**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 the doctor from your height and weight.

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

**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.

**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.

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 section 2).

**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 you stop using Fludara**

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 medicine, ask your doctor or pharmacist.

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Brand: FLUDARA IV 50MG IRELAND LEAFLET

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| Supersedes: | 505021 |
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## 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 side effects below are, ask your doctor to explain them to you.
Some side effects can be life-threatening. **Tell your doctor immediately:**

- ▶ 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.

**Below are possible side effects by how common they are**. **Very common side effects** (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 side effects** (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 side effects** (may affect up to 1 in 100 people)

- autoimmune disorder (see section 2)
- tumour lysis syndrome (see section 2)
- confusion
- lung toxicity, scarring 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 side effects** (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)

- bleeding in the brain
- 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)*).
- 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
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 Fludara

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 carton and vial label after "EXP". The expiry date refers to the last day of that month.
Unopened vials
This medicine does not require any special storage conditions.
Reconstituted and diluted solutions
Reconstituted Fludara should be used immediately or within 8 hours of reconstitution if stored at room temperature, or within 24 hours if stored at 2 °C to 8 °C.

## 6. Contents of the pack and other information

**What Fludara contains**

- ▶ The active substance is fludarabine phosphate. Each vial contains 50 mg fludarabine phosphate. 1 millilitre of reconstituted solution contains 25 mg fludarabine phosphate.
- ▶ The other ingredients are mannitol and sodium hydroxide.

**What Fludara looks like and contents of the pack**
Fludara is a sterile white powder for solution for injection or infusion provided in 10 ml glass vials. 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.

**Marketing Authorisation Holder and Manufacturer**
Marketing Authorisation Holder
Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden
The Netherlands
Manufacturer
Genzyme Ltd, 37 Hollands Road, Haverhill, Suffolk, CB9 8PU, UK

**Local representative:**
Sanofi Ireland Ltd. T/A SANOFI
Citywest Business Campus
Dublin 24
Tel: 01 4035 600
e-mail: IEmedinfo@sanofi.com

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

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| Belgium | Fludara |
| France | Fludara |
| Germany | Fludara |
| Greece | Fludara |
| Ireland | Fludara |
| Italy | Fludara |
| The Netherlands | Fludara |
| Portugal | Fludara |
| Spain | Beneflur |
| UK | Fludara |

**This leaflet was last revised in**
November 2015

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The following information is intended for healthcare professionals only:
Reconstitution
Fludara should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2 ml of sterile water for injection, the powder should fully dissolve in 15 seconds or less. Each ml of the resulting solution will contain 25 mg of fludarabine phosphate, 25 mg of mannitol, and sodium hydroxide (to adjust the pH to 7.7). The pH range for the final product is 7.2 - 8.2.
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%).
Inspection prior to use
The reconstituted solution is clear and colourless. It should be visually inspected before use.
Only clear and colourless solutions without particles should be used. Fludara should not be used in case of a defective container.
Handling and disposal
Fludara 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 Fludara 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 medicinal product, spillage or waste material should be disposed of in accordance with local requirements.

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| Packaging material name: | FLUDARA IV 50MG IRELAND LEAFLET |
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| Market regulatory validation | Cliodhna Carroll (Ireland regulatory team) | 15/02/2016 17:59:56 |
| Plant ready to print | Elizabeth Kirkham (Haverhill Packaging team) | 29/02/2016 11:21:26 |