Package leaflet: Information for the user

Fludara 10 mg film-coated tablets
Fludarabine phosphate

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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms 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 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 take Fludara

Do not take 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, before taking Fludara if you think any of these may apply to you.

Warnings and precautions
Talk to your doctor before taking 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 immediately.

  These may be signs of a reduction in the number of your blood cells, which may be caused either by the disease itself or the treatment. 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 treatment 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. 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 will Fludara will be stopped for further investigations. If the diagnosis of LE, ATL, or RPLS is confirmed, you 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. He/she may decide that you should start your treatment in hospital.

- **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 treatment.**

- **if you have or have had skin cancer** it may worsen or flare up again while you take Fludara or afterwards. You may develop skin cancer during or after Fludara treatment.

Other things to consider, when taking Fludara :

- **-Fludara must not be taken if you are pregnant** unless clearly indicated by your doctor.

- **Females: you must not become pregnant during treatment with Fludara and must use an effective method of contraception** during and for 6 months after end of treatment, because Fludara may be harmful for the unborn baby. If pregnancy occurs during your treatment, you must immediately inform your doctor. Your doctor will decide with you whether you should carry on taking Fludara.
- **Males: you are advised not to father a child and must use an effective method of contraception** during and at least for 3 months after end of treatment. You should seek advice on conservation of sperm prior to treatment because Fludara may alter male fertility**.**
- **You must not breast-feed** while you are treated 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 prescribed this medicine at all (see sections 2 and 3).

- **Fludara tablets may cause more vomiting and nausea** (being or feeling sick) than Fludara given intravenously. If this is a problem, your doctor will consider switching your treatment to the intravenous Fludara.

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 section 3. How to take 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

<u>Pregnancy</u>
Females: you must not become pregnant during treatment with Fludara 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 pregnancy occurs during your treatment, you

must immediately inform your doctor. Your doctor will decide with you whether you should carry on taking Fludara.

Breast-feeding**:**
You must not breast-feed while you are treated with Fludara.

Fertility in males and females
Females: you must use an effective method of contraception during and for 6 months after end of treatment, because Fludara may be harmful for the unborn baby.

Males: You are advised not to father a child and must use an effective method of contraception during and at least for 3 months after end of treatment. You should seek advice on conservation of sperm prior to treatment because Fludara may alter male fertility.

Both men and women who are planning to have a child after treatment are advised to talk to a doctor before start of Fludara treatment.

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 lactose
This medicine contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Fludara contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Fludara

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

How many tablets to take
The dose you should take 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 40 mg fludarabine phosphate/m^2 body surface area, once a day. The usual dose is between 3 to 10 tablets once a day. The exact number of tablets you should take is calculated by your doctor.

How to take Fludara tablets
Swallow the tablet whole with water. Do not break or chew the tablets. You can take Fludara either on an empty stomach or together with food.

How long you should take Fludara

Take the dose worked out by your doctor 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 blood tests after every treatment. Your individual dose will be carefully adjusted according to the number of your blood cells and your response to the treatment. If the number of your blood cells is too low, your next treatment cycle may be postponed for up to two weeks or your dose may be decreased. The dosage may also be decreased if side effects are a problem.

If you have been treated for two courses and you did not respond to the treatment but you also showed few symptoms of a reduced blood cell count, your doctor may decide to increase your dose.

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 your doctor may prescribe a lower dose. If your kidney function is severely reduced you will not be prescribed this medicine at all (see section 2).

If you take more Fludara than you should
Tell your doctor immediately if you took too many Fludara tablets
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 you forget to take Fludara
Talk to your doctor as soon as possible if you think you may have missed a dose or vomit after tablet taking.
Do not take a double dose to make up for the forgotten tablets.

If you stop taking Fludara
Do not stop taking Fludara without advice from your doctor.
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.

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, as known from Fludara for intravenous use.

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, website: www.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 bottle label and blister foil after "EXP". The expiry date refers to the last day of that month.

Fludara is a cytotoxic drug. It should always be stored in the original, child resistant container.

Do not store above 25°C. Do not refrigerate. Store in the original package to protect from moisture.

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.

Return any unused or waste tablets to your doctor or pharmacist. They will take care that Fludara is disposed of according to local requirements for cytotoxic drugs.

6. Contents of the pack and other information

What Fludara contains

- The active substance is fludarabine phosphate. Each film-coated tablet of Fludara contains 10 mg fludarabine phosphate.
- The other ingredients are
    - in the tablet core: cellulose (microcrystalline), lactose (monohydrate), silica (colloidal anhydrous), croscarmellose sodium, magnesium stearate;
    - in the film-coat: hypromellose, talc, titanium dioxide (E171), ferric oxide pigment (yellow (E172)), ferric oxide pigment (red (E172)).

What Fludara looks like and contents of the pack

Fludara are salmon-pink, capsule-shaped film-coated tablets, marked with 'LN' in a regular hexagon on one side.
The tablets are provided in blisters of 5 tablets each. The blisters are of polyamide/aluminium/poly-propylene thermoformable foil with a lidding foil of aluminium. The blisters are packed in a polyethylene tablet container with a child-resistent polypropylene screw cap.

Fludara is available in packs containing:
- 15 tablets in 3 blisters in a child-resistant bottle.
- 20 tablets in 4 blisters in a child-resistant bottle.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Genzyme Europe B.V.
Paasheuvelweg 25
1105 BP Amsterdam
Netherlands

Manufacturer

SANOFI WINTHROP INDUSTRIE, 30-36,
avenue Gustave Eiffel

37100 Tours, France.

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

Austria	Fludara
Denmark	Fludara
Finland	Fludara
France	Fludara
Greece	Fludara
Iceland	Fludara
Ireland	Fludara
Italy	Fludara
Luxembourg	Fludara
The Netherlands	Fludara
Norway	Fludara
Spain	Beneflur
Sweden	Fludara
UK	Fludara

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The following information is intended for healthcare professionals only:

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. Waste material may be disposed of by incineration.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic drugs.