**Package leaflet: Information for the patient**

Fludarabine 25 mg/ml Concentrate for Solution for Injection or Infusion

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 signs of illness 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 FLUDARABINE IS AND WHAT IT IS USED FOR

Fludarabine is a cytotoxic (anti-cancer medicine) medicine that inhibits the growth of cancer cells.

Fludarabine is used to treat chronic B-cell lymphocytic leukaemia (B-CLL), in patients with sufficient healthy blood cells production. First treatment for chronic lymphocytic leukaemia with Fludarabine phosphate should only be started in patients with advanced disease having disease related symptoms or evidence of disease progression.

CLL is a cancer of the lymphocytes (white blood cells).

If you are diagnosed with CLL, too many lymphocytes are produced. They either don't work properly or are too young (immature) to carry out the normal disease fighting functions of white blood cells. If there are too many of these abnormal cells they push aside (displace) healthy blood cells in the bone marrow (where most new blood cells are formed). They also displace the healthy blood cells in the blood and organs. Without enough healthy blood cells, infections, anaemia, bruising, excessive bleeding (haemorrhaging) or even organ failure can result.

## 2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE FLUDARABINE

**Do not take Fludarabine:**
- If you are allergic (hypersensitive) to Fludarabine phosphate or any of the other ingredients in this medicine (listed in section 6). If you are breast-feeding.
- If you have severe kidney problems. Your doctor will have told you if you have this condition.

**Warnings and precautions**
Talk to your doctor before using Fludarabine.

Take special care with Fludarabine

- **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 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 Fludarabine before. During treatment with Fludarabine 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 Fludarabine.

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

  If Fludarabine 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 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 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 Fludarabine 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.

- **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 Fludarabine. 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 (or have been).**

- **if you need a blood transfusion and you are being treated with Fludarabine (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 therapy or afterwards. You may develop skin cancer during or after Fludarabine therapy.

**Other things to consider, while you are treated with Fludarabine**

- **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 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 if clearly necessary.

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

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

- **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 Fludarabine in children below the age of 18 years has not been established. Therefore, Fludarabine is not recommended for use in children.

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

**Other medicines and Fludarabine**
Please tell your doctor if you are taking, or have recently taken any other medicines.

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. It may reduce the effectiveness of Fludarabine.

- **cytarabine (Ara-C)** is used to treat chronic lymphatic leukaemia. If fludarabine phosphate is combined with cytarabine, levels of the active form of fludarabine phosphate in leukemic 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
Fludarabine 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 Fludarabine if clearly necessary.

Breast-feeding
You must not start or continue breast feeding during your treatment with Fludarabine 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.

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

Fludarabine contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 45mg (average dose), that is to say essentially 'sodium-free'.

## 3. HOW TO TAKE FLUDARABINE

**Children and adolescents**
Fludarabine is not recommended for children and adolescents.

**Dosage**
**The recommended dose is 25 mg/m$^2$ body surface.**
The dose you are given depends on your body surface area. This is measured in square metres (m$^2$) and is worked out from your height and weight.

**Methods and routes of administration**
Fludarabine will be given either as **an injection** (into a vein) or as **an infusion** (with a drip). One infusion takes approximately 30 minutes.
Your doctor will make sure that Fludarabine is not given beside the vein (paravenously). However, if this happens, no severe local adverse events have been reported.

**Duration of treatment**
The dose will be given once a day for 5 consecutive days.
This five-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 Fludarabine. 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 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.

**If you take more Fludarabine than you should:**
There is no specific antidote for Fludarabine overdosage. If you may have received too much Fludarabine, the doctor will stop the therapy and treat the symptoms.
High doses can lead to a severely reduced number of blood cells.
For Fludarabine given intravenously it has been reported, that overdose can cause delayed blindness, coma and even death.

**If you forget to take Fludarabine is forgotten:**
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 stop using Fludarabine**
You and your doctor may decide to stop your treatment with Fludarabine 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 notice sudden wheeziness, difficulty in breathing, swelling of the eyelids, face or lips, rash or itching (especially affecting your whole body) as this could be signs of an allergic reaction

- 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.*

- 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.

The following side effects have been reported:

**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, diarrhoea, 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 disorders (see section 2);
- tumour lysis syndrome (see section 2);
- 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 the 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
- 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.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

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

Store Fludarabine in a refrigerator (2°C – 8°C).

Storage of Fludarabine after dilution - see section "Information for medical and healthcare professionals".

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 ml contains 25 mg fludarabine phosphate.
- The other ingredients are disodium phosphate dihydrate, sodium hydroxide, and water for injection.

**What Fludarabine looks like and contents of the pack**

Fludarabine is a clear, colourless to almost colourless solution.

Fludarabine is packed in glass vials with 1 x 2 ml, 5 x 2 ml and 10 x 2 ml concentrate for solution for injection or infusion.

It is available in packs containing 1 vial, 5 vials or 10 vials with or without a plastic protection (Onco-Safe or Sleeving) "Onco-Safe" and Sleeving do not come into contact with the medicine and provide additional transport protection, which increases the safety for the medical and pharmaceutical personnel.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder:**

Sandoz Limited
Park View, Riverside Way
Watchmoor Park
Camberley, Surrey
GU15 3YL
United Kingdom

**Manufacturer:**

Ebewe Pharma Ges.m.b.H. Nfg. KG
Mondseestraße 11, A-4866 Unterach,
Austria

**This leaflet was last revised in 07/2021.**

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**Other sources of information**

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

Fludarabine 25 mg/ml - concentrate for solution for injection or infusion

**Instructions for use and handling and disposal**

<u>Dilution</u>

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

Inspection prior to use

Only clear and colourless solutions without particles should be used. The product should not be used in case of a defective container.

Handling and disposal

Pregnant women should be excluded from handling fludarabine phosphate. The Regulations concerning proper handling and disposal must be followed considering guidelines for proper handling and disposal of cytotoxic medicinal products. Any spilled or unused material may be eliminated by incineration.

Caution should be exercised during handling and preparation of fludarabine phosphate solution. The use of protective gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage. If the solution comes in contact with skin or mucous membranes, the affected area should be cleaned thoroughly with soap and water.

The medicinal product is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

**FOR INTRAVENOUS USE ONLY.**

**Incompatibilities:**

It is not recommended to mix up fludarabine solutions with other drugs or other solutions except physiological saline under aseptic conditions.

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

**Administration:**

It is strongly recommended that Fludarabine should be only administered intravenously. No cases have been reported in which relevant local irritation was observed after paravenous administration. However, pareavenous administration should be avoided.

**Storage and shelf life:**

*As packaged for sale:*
Store in a refrigerator (2°C – 8°C).

*Shelf life after dilution:*
Infusion solutions cited above are physically and chemically stable for at least 28 days when stored in a refrigerator (2-8°C) with protection from light and at room temperature (20°C-25°C) with and without protection from light.
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 would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.