Fludarabine®
Phosphate NEAPOLIS

FLUDARABINE PHOSPHATE 25mg/ml

Concentrate for injection or for infusion - Fludarabine phosphate

Read 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, pharmacist or nurse.
- 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, pharmacist or nurse. This applies to any side effect that is not mentioned in this leaflet. See section 4.

What is in this leaflet ? :

1. What is FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, Concentrate for injection or for infusion and in which case is it used ?
2. What you need to know before you take FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, Concentrate for injection or for infusion ?
3. How to take FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, Concentrate for injection or for infusion ?
4. Possible side effects ?
5. How to store FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, Concentrate for injection or for infusion ?
6. Additional information.

1. WHAT IS FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, Concentrate for injection or for infusion AND IN WHICH CASE IS IT USED ?

Pharmacotherapeutic Class

FLUDARABINE PHOSPHATE NEAPOLIS contains the active substance fludarabine phosphate which prevents the development of new cancer cells. All cells in the body are produced by dividing new cells resembling them. FLUDARABINE PHOSPHATE NEAPOLIS is absorbed by cancer cells and blocks their division.

When cancer cells in the white blood cells (chronic lymphocytic leukemia) occurs, the body produces many abnormal white blood cells (lymphocytes) and the lymph nodes begin to swell in various parts of the body. Abnormal white blood cells cannot carry out their normal role of fighting disease. If there are too many abnormal white blood cells, they eventually replace healthy blood cells, which can cause infections, a decrease in the number of red blood cells (anemia), bruising, abnormally heavy bleeding, or even organ failure.

Therapeutic indications

FLUDARABINE PHOSPHATE NEAPOLIS is used for the treatment of B-cell chronic lymphocytic leukemia (CLL) in patients with sufficient production of healthy blood cells.

FLUDARABINE PHOSPHATE NEAPOLIS should be used as the first treatment for chronic lymphocytic leukemia only in patients with advanced disease with symptoms of the disease or with evidence of worsening of the disease.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, Concentrate for injection or for infusion ?

List of needed information before taking the medicine

Not applicable.

Contraindications

Never use FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml :

- **if you are allergic** to fludarabine phosphate or any of the other components of this medicine (listed in section 6).
- **if you breastfeed,**
- **if you have severe kidney problems,**
- **if your red blood cell count is reduced due to some type of anemia** (decompensated hemolytic anemia).

Your doctor will have told you if you have this condition.

If you think any of these apply to you, **tell your doctor**

Precautions for use ; special warnings

Warnings and precautions

Talk to your doctor before taking FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml

Take special care with FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml :

- **if your bone marrow is not working properly or if your immune system is depressed or functioning poorly** or if you have a history **of serious infections,**

your doctor may decide not to treat you with this medicine or take preventive measures.

- **if you feel really bad, if you notice any unusual bruising, abnormally heavy bleeding from injuries, or if you think you are getting a lot of infections,**
- **if during treatment your condition is red to brownish in color, or if you have rashes or blisters on your skin,**

Tell your doctor immediately.

These symptoms may indicate a decrease in the number of red blood cells, which may be due to the disease itself or to treatment. They can last up to a year, whether or not you have received treatment with FLUDARABINE PHOSPHATE NEAPOLIS before. During treatment with FLUDARABINE PHOSPHATE NEAPOLIS, it's also possible that **your immune system attacks various parts of your body or your red blood cells** (Called "autoimmune disorder »). If necessary, the vital prognosis may be at stake.

If this happens to you, your doctor will stop treatment and you may receive other treatment such as transfusion of irradiated blood (see below) and corticosteroids.

You will be subjected to regular blood tests during treatment and you will be closely monitored for the duration of your treatment with FLUDARABINE PHOSPHATE NEAPOLIS.

- if you notice any unusual symptoms in your nervous system, such as visual disturbances, headache, confusion, seizures.

Regarding the prolonged administration of FLUDARABINE PHOSPHATE NEAPOLIS : the long-term effects of the drug on the central nervous system are not known. However, patients who have undergone up to 26 treatments at the recommended dose have been able to tolerate it.

When FLUDARABINE PHOSPHATE NEAPOLIS is given at the recommended dose, after or with other medicines, the following side effects have been reported:

Neurological disorders manifested by headache, urge to vomit (nausea) and vomiting, seizures, visual disturbances including loss of vision, changes in mental state (abnormal thoughts, confusion, altered consciousness) and occasionally neuromuscular disorders manifested by muscle weakness in your limbs (including partial or total paralysis) (symptoms of leukoencephalopathy, acute toxic leukoencephalopathy or reversible posterior leukoencephalopathy syndrome (RPLS)).

Blindness, coma and death have been reported following **the administration of a dose four times higher than the recommended dose.** Some of these symptoms appeared remotely, about 60 days after stopping treatment.

Cases of leukoencephalopathy (LE), acute toxic leukoencephalopathy (ATL) or reversible posterior leukoencephalopathy syndrome (RPLS), associated with the same symptoms as those described above, have also been reported in patients receiving FLUDARABINE at doses greater than the recommended dose.

LE, ATL, and RPLS can be irreversible, life-threatening, or fatal.

As soon as an LE, ATL or RPLS is suspected, treatment with FLUDARABINE PHOSPHATE NEAPOLIS will be stopped and examinations will be performed. If the diagnosis of LE, ATL or RPLS is confirmed, your doctor will stop your treatment with FLUDARABINE PHOSPHATE NEAPOLIS permanently.

- if you feel pain in your flanks, if you notice blood in your urine or a decrease in the volume of your urine,

- When **the disease is very severe, your body may not be able to eliminate all the waste products** resulting from the destruction of your cells by FLUDARABINE PHOSPHATENEAPOLIS. This reaction is called tumor lysis syndrome : it is likely **to cause kidney failure as well as heart problems and may occur within the first week of treatment.** Your doctor is aware of this phenomenon and may give you other medicines to help prevent it.

- if you are to have a stem cell sample and that you are on treatment with FLUDARABINE PHOSPHATE NEAPOLIS (or if you have been).

- if you are going to have a blood transfusion and are on treatment with FLUDARABINE PHOSPHATE NEAPOLIS (or if you have been).

If you need a blood transfusion, your doctor will ensure that you are either exclusively transfused blood treated by irradiation. Transfusions of unirradiated blood can cause serious complications or even death.

- if you notice any changes in your skin, either during or after taking this medicine,

- if you have a skin cancer (or if you had one), it may get worse or experiencing a new surge during treatment with FLUDARABINE PHOSPHATE NEAPOLIS or after it. It is possible that you develop a skin cancer during or after treatment with FLUDARABINE PHOSPHATE NEAPOLIS.

Other issues to be considered during treatment with FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml :

- Men and women of childbearing potential must use effective contraception during treatment and for the next 6 months. It cannot be excluded that this medicine has harmful effects on an unborn child. Your doctor will carefully evaluate the benefit of your treatment against the risk to the unborn child, and if you are pregnant, he will prescribe FLUDARABINE PHOSPHATE NEAPOLIS only if clearly needed.

- if you plan to breastfeed or if you are breastfeeding, you should not start or continue breastfeeding while taking FLUDARABINE PHOSPHATE NEAPOLIS.

- if you need to get vaccinated, ask your doctor for advice as any live vaccine should be avoided during and after treatment with FLUDARABINE PHOSPHATE NEAPOLIS.

- If you have kidney problems or are over the age of 65, you will have regular blood and / or laboratory tests to check how your kidneys are working. If you have severe kidney problems, you should not take this medicine (see sections 2 and 3).

Children and adolescents :

The safety and efficacy of FLUDARABINE in children under 18 years of age have not been established. It is therefore not recommended to use FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml in children.

Elderly patients and FLUDARABINE PHOSPHATE NEAPOLIS :

If you are over 65, you will have regular checkups to check your kidney function (see also section 3 "How to take FLUDARABINE PHOSPHATE NEAPOLIS »).

If you are over 75, you will be closely monitored.

Interactions with other medicines

FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml and other medicines :

If you are taking or have recently taken any other medicines, including medicines obtained without a prescription, tell your doctor. It is especially important if you are taking any of the following medicines :

- Pentostatin (deoxycoformycin), also used to treat chronic lymphocytic leukemia B cells. The combination of these two substances can lead to serious pulmonary complications.

- Dipyridamole and other similar substances, which are used to prevent excessive clotting. They may decrease the effectiveness of FLUDARABINE PHOSPHATE NEAPOLIS.

- Cytarabine (Ara-C) prescribed for the treatment of chronic lymphoid leukemia. The combination of FLUDARABINE PHOSPHATE NEAPOLIS with cytarabine may increase the concentration of the active substance in FLUDARABINE PHOSPHATE NEAPOLIS in leukemia cells. However, no change has been observed to date in the overall concentration of the substance in the blood or its elimination from the blood.

Interactions with food and drinks

Not applicable.

Interactions with phytotherapy products or alternative therapies

Not applicable.

Use during pregnancy and breastfeeding

Pregnancy, breastfeeding and fertility

Pregnancy

FLUDARABINE PHOSPHATE NEAPOLIS should not be administered to pregnant patients because studies in animals and very limited experience in humans have shown possible risks of malformations in the unborn child and the possibility of miscarriage, early pregnancy or premature birth.

If you pregnant or think you may be, tell your doctor immediately.

Your doctor will carefully evaluate the benefit of your treatment against the possible risk to the unborn child, and if you are pregnant, he will only prescribe FLUDARABINE PHOSPHATE NEAPOLIS if clearly needed.

Breastfeeding

You should not start or continue breastfeeding while taking FLUDARABINE PHOSPHATE Neapolis as this medicine may interfere with your baby's growth and development.

Ask your doctor for advice before taking any medicine.

Fertility

If you are a woman or a man of childbearing age, you should use effective contraception during treatment and for at least the next 6 months.

Sports

Not applicable.

Effects on the ability to drive or use machines

Driving and using machines

Some people taking FLUDARABINE PHOSPHATE NEAPOLIS may feel tired or weak, have vision problems, become confused or restless, or have seizures. Therefore, do not drive or use machines until you are sure you do not have this type of condition.

List of excipients with known effect

FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml contains sodium

This medicine contains less than 1 mmol of sodium per dose, i.e. it is essentially sodium-free.

3. HOW TO TAKE FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, Concentrate for injection or for infusion?

Instructions for proper use

As an indication, the recommended dose is 40 mg / m2 of body surface area per day, as a treatment for 5 consecutive days every 28 days.

Dosage, Mode and / or route (s) of administration, Frequency of administration and Duration of treatment

FLUDARABINE PHOSPHATE NEAPOLIS should be administered under the supervision of a qualified doctor with experience in the field of cancer treatments.

How much FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml is it administered?

The dose you will receive will depend on your body surface area. This is measured in square meters (m2) and is defined by your doctor based on your height and weight.

The recommended dose is 25 mg of fludarabine phosphate / m2 of body surface.

How is FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml administered ?

FLUDARABINE PHOSPHATE NEAPOLIS is administered as a solution for injection or, more often, as an infusion.

An infusion involves introducing medication directly into the bloodstream by drip into the vein. Each infusion lasts approximately 30 minutes.

Your doctor will take care not to inject FLUDARABINE PHOSPHATE NEAPOLIS beside the vein (paravenous injection). If this should happen, note that no serious local adverse reactions have been reported.

How long FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml is administered ?

The dose will be administered once a day for 5 consecutive days.

This cure of 5 days treatment will be repeated every 28 days until your doctor determines that the best effect was achieved (usually after 6 treatments).

The duration of treatment depends on its success and how you support FLUDARABINE PHOSPHATE NEAPOLIS, repetition of the treatment may be delayed if side effects are a problem.

You will be subjected to regular blood tests during treatment. The dose that will be administered will be carefully adjusted according to your blood counts and your response to treatment.

Dosage may be reduced if side effects are a problem.

If you have kidney problems or are over 65, you will have regular checkups to check your kidney function. If your kidneys are not working properly, you may be given a lower dose of this medicine. If you have severe kidney failure you will not be able to receive this medicine at all (see section 2).

In case of accidental spillage of the solution FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml

If the solution comes into contact with your skin or mucous membranes of your nose and mouth, the affected area should be washed thoroughly with soap and water. In case of contact with eyes, rinse them thoroughly with copious amounts of tap water. Avoid inhalation of the product.

Symptoms and instructions in case of overdose

If FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml was administered in large quantities :

If you may have received an overdose, your doctor **will** stop treatment and **will treat symptoms.**

Using high doses can also lead to a serious decrease in the number of blood cells. Overdose may lead to delayed blindness, coma, and even death

Instructions if one or more doses are missed

If a dose of FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml has been missed :

Your doctor will set the medicine administration schedule. If you think a dose may have been missed, see your doctor as soon as possible.

Risk of withdrawal syndrome

If you stop using FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml :

You and your doctor may decide to stop treatment with FLUDARABINE PHOSPHATE NEAPOLIS if the side effects get too serious.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist for more information.

4. POSSIBLE SIDE EFFECTS ?

Description of side effects

Like all medicines, this medicine can have side effects, although not everybody gets them. If you are not sure about what the below side effects 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, coughing, or chest pain with or without fever. These symptoms may indicate lung problems,

- if you notice any unusual bruising, abnormally heavy bleeding from injury, or if you think you are getting a lot of infections. This may be due to a drop in your blood count. This can also increase the risk of (serious) infections due to organisms that normally do not cause disease in healthy people (opportunistic infections), including the reactivation of latent viruses such as the Herpes virus.

- If you feel pain in the flanks, if you notice blood in your urine or decrease in the volume of your urine, These symptoms may be signs of tumor lysis syndrome (see section 2).

- If you notice a reaction of the skin or mucous membranes with redness, inflammation, blistering and erosion, This may be a sign of a very serious allergic reaction (Lyell syndrome, Stevens-Johnson syndrome).

- if you have palpitations (if you suddenly experience a racing heart) or chest pain. These may be signs of heart problems.

Below are the possible side effects listed depending on the frequency of these effects.

Very common side effects (may affect more than 1 in 10 people) :

- Infections (some of which are serious).
- Infections due to depression of the immune system (such as opportunistic infections).
- Lung infections (pneumonia) with possible symptoms such as difficulty breathing and / or cough with or without fever.
- Decrease in the number of blood platelets (thrombocytopenia) with the possibility of bruising and bleeding.
- Decrease in the number of white blood cells (neutropenia).
- Decrease in the number of red cells (anemia).
- Cough.
- Vomiting, diarrhea, feeling sick (nausea).
- Fever.
- Fatigue.
- Asthenia.

Common side effects (may affect up to 1 in 10 people) :

- Other blood cancers (myelodysplastic syndrome, acute myeloid leukemia). Most patients with these diseases have been previously treated or are being treated concomitantly or have been lately treated with other anticancer agents (alkylating agents, topoisomerase inhibitors) or with radiation.
- Bone marrow dysfunction (myelosuppression).
- Severe loss of appetite leading to weight loss (anorexia).
- Numbness or weakness of the limbs (peripheral neuropathy).
- Vision disorders.
- Inflammation of the inside of the mouth (stomatitis).
- Skin rash.
- Swelling due to excessive fluid retention (edema).
- Inflammation of the mucous membranes of the digestive system, from the mouth to the anus (mucositis).
- Chills.
- General feeling of discomfort.

Uncommon side effects (may affect up to 1 in 100 people) :

- Autoimmune disorders (see section 2).
- Tumor lysis syndrome (see section 2).
- Confusion.
- Pulmonary toxicity, scarring of interstitial tissues of the lungs (pulmonary fibrosis), pulmonary inflammation (pneumonia), shortness of breath (dyspnea).
- Bleeding from the stomach and intestines.
- Abnormal liver or pancreatic enzyme levels.

Rare side effects (may affect up to 1 in 1,000 people) :

- Lymphatic system disorders due to viral infection (EBV-related lymphoproliferative disease).
- Coma.
- Convulsive seizures.
- restlessness.
- Blindness.
- Inflammation or deterioration of the optic nerve (optic neuritis ; optic neuropathy).
- Heart failure.
- Irregular heartbeat (arrhythmia).
- Skin cancer.
- Skin and / or mucous membrane reaction with redness, inflammation, blistering and erosion (Lyell syndrome, Stevens-Johnson syndrome).

Unknown frequency (cannot be estimated from the available data)

- Cerebral hemorrhage.
- Neurological disorders manifested by headaches, feeling sick (nausea) and vomiting, seizures, visual disturbances including vision loss, changes in mental status (abnormal thinking, confusion, impaired consciousness) and occasionally neuromuscular disorders manifested by muscle weakness in your limbs (including partial or total paralysis) (symptoms of leukoencephalopathy, acute toxic leukoencephalopathy or reversible posterior leukoencephalopathy syndrome (RPLS).
- Pulmonary hemorrhage.
- Inflammation of the bladder that can cause pain when urinating and blood in the urine (hemorrhagic cystitis).

Reporting side effects

If you experience any side effect, whether or not it is mentioned in this leaflet, tell your doctor, pharmacist or other healthcare professional (nurse, etc.) immediately. You can also report this side effect directly to the Regional Pharmacovigilance Center. By reporting side effects you can help improve knowledge of the safety of this medicine.

5. HOW TO STORE FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, Concentrate for injection or for infusion?

Keep this medicine out of the sight and reach of children.

Expiry date

Do not use this medicine after the expiry date which is stated on the bottle and carton label after EXP. The expiration date refers to the last day of the month.

Fludarabine®
Phosphate NEAPOLIS

FLUDARABINE PHOSPHATE 25mg/ml

Concentrate for injection or for infusion - Fludarabine phosphate

Storage conditions

Unopened vials

Store in the refrigerator (between 2 ° C and 8 ° C).

Diluted solution

The solution should be used immediately.

In the event of non-immediate use, the diluted solution of FLUDARABINE PHOSPHATE NEAPOLIS 50mg / 2ml is stable in 10ml, and 125 ml, of 0.9% sodium chloride (NaCl) solution and 5% dextrose solution for 8 hours at room temperature or for 24 hours at a temperature between 2 ° C and 8 ° C

If necessary, warnings against some visible signs of deterioration

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist what to do with unused medicine. These measures will help protect the environment.

6. ADDITIONAL INFORMATION

Complete list of active substances and excipients

What does FLUDARABINE PHOSPHATE NEAPOLIS 25mg / ml, Concentrate for injection or for infusion **contain ?**

The active substance is : fludarabine phosphate.

Each vial contains 50 mg of fludarabine phosphate. One milliliter of solution contains 25 mg of fludarabine phosphate.

The other components are : mannitol, sodium hydroxide, Water for injections.

Pharmaceutical form and content

What does FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, Concentrate for injection or for infusion look like and content of the outer packaging ?

FLUDARABINE PHOSPHATE NEAPOLIS is a concentrate for injection or for infusion, clear, colorless or slightly brown-yellow supplied in type I glass vials in a box of 1 vial.

Supply conditions : Table A List I

M.A.N° :

FLUDARABINE PHOSPHATE NEAPOLIS 25mg/ml, box of 1 vial: 939 312 1H

Marketing and autorisation holder and manufacturer

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THIS IS A MEDICINE

- A medicine is not like other consumer goods.
- A medication is a product that affects your health and its consumption without compliance to the prescription exposes you to danger.
- You should strictly follow your doctor's prescription and directions for use, as well as the advice of your pharmacist.
- Your doctor and pharmacist are familiar with the medication, its indications and contraindications.
- Do not stop treatment on your own during the prescribed period
- Do not resume, do not increase doses without consulting your doctor .

KEEP MEDICINES OUT OF THE REACH OF CHILDREN

The following information is only intended for healthcare professionals :

Dilution :

The required dose (calculated based on the patient's body surface area) must be drawn up using a syringe. For a bolus injection, this dose should be diluted in 10 ml of sodium chloride 9 mg / ml (0.9%). When administered by infusion, the required dose should be diluted in 100 ml of sodium chloride 9 mg / ml (0.9%) and infused in approximately 30 minutes.

In clinical studies, the product was diluted in 100 ml or 125 ml of 5% dextrose solution or 9 mg / ml sodium chloride (0.9%).

Mirage before use :

The solution is clear, colorless to slightly brown-yellow. It must be candled before use. Only these particle-free solutions can be used. FLUDARABINE PHOSPHATE NEAPOLIS should not be used if the container has been damaged.

Handling and destruction :

FLUDARABINE PHOSPHATE NEAPOLIS should not be handled by pregnant women.

Appropriate handling and destruction procedures must be followed in accordance with applicable regulations for cytotoxic medicines.

Precautions should be taken when handling and preparing the FLUDARABINE PHOSPHATE NEAPOLIS solution. Wearing latex gloves and safety glasses is recommended in order to avoid exposure to the product in the event of a broken bottle or other incident. In the event of accidental contact with the skin or mucous membranes, wash the affected areas thoroughly with soap and water. In the event of accidental projection in the eyes, rinse thoroughly with water. Inhalation of the product should be avoided.

This medication is for single use only. Any fraction of unused product, accidental spillage or waste must be disposed of in accordance with current laws.

NEAPOLIS PHARMA

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