Package leaflet: Information for the user

Isovorin 10 mg/ml, solution for injection

Levofolinic acid

Read all of this leaflet carefully before you are given 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 any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

What is in this leaflet:

1. What Isovorin is and what it is used for
2. What you need to know before you are given Isovorin
3. How Isovorin is given
4. Possible side effects
5. How to store Isovorin
6. Contents of the pack and other information

1. What Isovorin is and what it is used for

Isovorin is used to reduce adverse events during high dose treatment with methotrexate (a chemotherapeutic agent).

Isovorin is used in combination with 5-fluorouracil for treatment of cancer of the colon or rectum.

2. What you need to know before you are given Isovorin

Do not use Isovorin:
- If you are allergic (hypersensitive) to levofolinic acid or any of the other ingredients of Isovorin.
- If you have a blood disease called anaemia caused by lack of Vitamin $B_{12.}$

Take special care with Isovorin:
- If you are pregnant, think you might be pregnant or are breast feeding.
- If you are taking, or have recently taken any other medicines. In particular, you should tell your doctor if you are taking other medicines for the treatment of epilepsy (see also “Taking other medicines”).
- If you have macrocytosis (larger red blood cells than normal).

Isovorin may mask a certain type of blood disease (anaemia) caused by a lack of Vitamin $B_{12.}$

If your kidney function is reduced due to a pre-existing condition or due to previous use of methotrexate, your doctor may ordinate higher dose or longer treatment with Isovorin.

If you are treated with Isovorin and 5-flourouracil and get diarrhoea you should immediately inform your doctor. The treatment with 5-fluorouracil may be continued with a lower dose or stopped.

Taking other medicines:
Isovorin may alter the effect of certain medicines used for:

- infections (folic acid antagonists e.g. cotrimoxazole and pyrimethamine)
- cancer (5-fluorouracil)
- epilepsy (phenobarbital, phenytoin, primidone or succinimides) as the effect of these medicines may be reduced and seizures may increase.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Pregnancy
There is limited experience in using Isovorin during pregnancy but the risk of using folic acid during pregnancy is considered to be small. Methotrexate and 5-fluorouracil should not be used during pregnancy and lactation unless prescribed by the doctor on strict indication. This also applies to the use of Isovorin together with methotrexate or 5-fluorouracil. Ask you doctor or pharmacist for advice before taking any medicine

Breast-feeding
It is not known whether Isovorin passes into milk. Ask you doctor for advice before breast-feeding.

Driving and using machines
No effects on the ability to drive and use machines have been observed.

3. How Isovorin is given

Isovorin will always be prepared and given to you by a doctor or another healthcare professional as an intravenous or intramuscular injection (into your vein or muscle).

Isovorin must not be injected into your spine (intrathecally)

When used to reduce the adverse events of methotrexate, your treatment will usually start 24 hours after your methotrexate treatment starts. The usual dose of Isovorin is about 7.5 mg every 6 hours for 10 doses. The dose is calculated in relation to your body surface. However, your doctor may decide to change this, depending on your condition and the dose of methotrexate you have already received. During your treatment your doctor may also wish to take blood samples from you.

When used in combination with 5-fluorouracil, for the treatment of cancer of the colon or rectum, a dose will be given to you of 100 mg Isovorin daily for 5 days. The dose is calculated in relation to your body surface. The five days treatment may be given with an interval of 4 weeks (28 days) in 2 turns and thereafter with an interval of 4-5 weeks (28-35 days).

If too much Isovorin is given or if you miss a dose

As this medicine is prepared and given by a healthcare professional, it is unlikely you will be given too much.

If you are concerned about this, or think you may have missed a dose, tell your doctor immediately.

4. Possible side effects

Like all medicines, Isovorin can cause side effects, although not everybody gets them.

The following side effects may occur in patients treated with Isovorin:

Very rare: may affect up to 1 in 10,000 people
- Severe allergic reaction - you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint. This is a serious side effect. You may need urgent medical attention.
- Nettle-rash (urticaria)

Uncommon: may affect up to 1 in 100 people
- Fever

Rare: may affect up to 1 in 1,000 people
- An increase in convulsions (fits) in patients with epilepsy
- Depression
- Agitation
- Problems with the digestive system
- Difficulty sleeping (insomnia)

Not known: frequency cannot be estimated from the available data
- Toxic Epidermal Necrolysis (TEN): A severe skin disorder including loss of the skin
- Steven-Johnson Syndrome (SJS): A severe skin disorder including blister shaped rash and inflammation of the skin, particularly on the hands and feet and around the mouth accompanied by fever

If you receive Isovorin in combination with an anticancer medicine containing fluoropyrimidines, it is more likely that you experience the following side effects of this other medicine:

Very common: may affect more than 1 in 10 people
- Nausea
- Vomiting
- Severe diarrhea
- Drying out which may be due to diarrhea
- Inflammation of the lining of the intestine and mouth (life-threatening conditions have occurred)

Common: may affect up to 1 in 10 people
- Redness and swelling of the palms of the hands or the soles of the feet which may cause the skin to peel (hand-foot syndrome)

Not known: frequency cannot be estimated from the available data
- Reduction in the number of blood cells (including life-threatening conditions)
- Elevated blood ammonia levels

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

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. * By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Isovorin

Store in a refrigerator (2°C – 8°C).

Keep out of the reach and sight of children.

Do not use Isovorin 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.

Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. Contents of the pack and other information

What Isovorin contains

- The active substance is levofolinic acid.
- The other ingredients are sodium chloride, hydrochloric acid and sodium hydroxide (for pH adjustment), water for Injection

What Isovorin looks like and contents of the pack

Isovorin is a clear, yellowish solution which is essentially free from visible particles.

Each pack of Isovorin contains one vial of either 2.5 ml, 5 ml or 17.5 ml.

Each vial contains either 25mg, 50mg or 175mg of the active ingredient calcium levofolinate in 2.5ml, 5ml and 17.5ml respectively.

Marketing Authorisation Holder

<[To be completed nationally]>
Manufacturer
Wyeth Lederle S.p.A.
Via Franco Gorgone
Zona Industriale
95100 Catania, Italy

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

Sweden, Finland - Isovorin 10 mg/ml solution for injection

This leaflet was last revised in {MM/YYYY} 2016-06-08

<[To be completed nationally]>

<Other sources of information>

<Detailed information on this medicine is available on the website of {MS/Agency}>

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

- Isovorin should only be given by intramuscular or intravenous injection and must not be administered intrathecally.

- The time of infusion is usually dependent on the dosage, which varies, so no general guidelines can be given. The administration of Isovorin should be started 24 hours after already begun therapy with methotrexate.

- Inspect the solution visually before use. The solution for injection should be clear and yellowish. Do not use Isovorin if you notice that the solution is cloudy or if particles are observed. Discard the solution if cloudy or if particles are observed.

- Isovorin is intended only for single use. Any unused portion of the solution should be disposed of in accordance with the local requirements.

- **Incompatibilities**
  Incompatibilities have been reported between injectable forms of calcium folinate and injectable forms of fluorouracil and methotrexate.

  Fluorouracil
  Calcium folinate must not be mixed in the same infusion as 5-fluorouracil because a precipitate may form. Fluorouracil 50 mg/mL with calcium folinate 20 mg/mL, with or without dextrose 5% in water, has been shown to be incompatible when mixed in different amounts and stored at 4°C, 23°C, or 32°C in polyvinyl chloride containers.