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Package leaflet: Information for the user

Calcium folinate 10 mg/ml solution for injection/infusion

folinic 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 nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Calcium folinate is and what it is used for

Calcium folinate 10 mg/ml solution for injection/infusion contains the active substance folinic acid as calcium folinate hydrate (further referred to as calcium folinate). Calcium folinate is a calcium salt of folinic acid. It belongs to a group of medicines called 'detoxifying agents'.

This medicine is used to:
- reduce the harmful effects and treat overdose of certain anticancer medicines such as methotrexate and other folic acid antagonists in adults and children. This procedure is known as "calcium folinate rescue";
- treat cancer in combination with fluorouracil (an anticancer medicine). Fluorouracil works better when given with calcium folinate.

2. What you need to know before you are given Calcium folinate

You should not be given Calcium folinate
- if you are allergic to calcium folinate or any of the other ingredients of this medicine (listed in section 6);
- if you have a type of anaemia (not enough red blood cells) caused by lack of vitamin B_{12}.

If you are not sure if any of the above applies to you, talk to your doctor or nurse before this medicine is given to you.

You should not be given Calcium folinate together with certain anticancer drugs if you are pregnant or breast-feeding (your doctor will know which these are).

This medicine must not be injected into the spine (intrathecally).

Warnings and precautions
Talk to your doctor or nurse before you are given this medicine if:
- you have kidney disorders (you may need a higher dose or need this medicine for longer period of time);
- you have epilepsy.

<u>Use of calcium folinate with fluorouracil</u>
You should not receive this medicine together with fluorouracil if you have noticed that your medicine is causing problems to your stomach and gut.

In case you should receive calcium folinate and fluorouracil at the same time talk to your doctor or nurse before you are given this medicine if:
- you have had radiotherapy;
- you have stomach or bowel disorders;
- you have an inflammation on the inside of your mouth;
- you are elderly;
- you feel very weak.

Your doctor will monitor how well your liver and/or kidneys are working and will take regular blood tests to check this.

Other medicines and Calcium folinate
Tell your doctor or nurse if you are using, have recently used or might use any other medicines.

This is particularly important if you are using any of the following medicines as special care is needed:
- medicines known as **folic acid antagonists**, such as co-trimoxazole (an antibiotic) or pyrimethamine (used to treat malaria). Calcium folinate may reduce or fully counteract the effect of these medicines;
- **fluorouracil** (anticancer medicine). Calcium folinate enhances the effectiveness and also side effects of fluorouracil;
- **medicines to treat epilepsy** (phenobarbital, phenytoin, primidone or succinimides e.g. ethosuximide). Calcium folinate may reduce the effect of these medicines. Your doctor may check blood levels of these medicines and change your dose to prevent increased convulsions (fits).

Pregnancy and breast-feeding
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 being given this medicine.
Calcium folinate does not induce harmful effects if used as the only medicine during pregnancy.
You must not be given Calcium folinate together with fluorouracil while pregnant or breast-feeding as it might harm the baby.
You will only be given Calcium folinate together with methotrexate when pregnant or breast-feeding if your doctor thinks it is necessary.

Driving and using machines
There is no evidence that calcium folinate has any effect on the ability to drive or use machines.

Calcium folinate contains sodium
This medicine contains 3.15 mg sodium (main component of cooking/table salt) in each ml of solution. This is equivalent to 0.16 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Calcium folinate

This medicine may be given by injection or infusion (drip) into a vein, or as an injection into a muscle. If it is given by infusion this medicine will be diluted first.

Your doctor will determine the correct dose of this medicine for you and how often it must be given. It will depend upon the medical condition which is being treated, your body surface area and any other treatment you may be receiving.

If you are given more Calcium folinate than you should
This medicine will be given to you in a hospital, under the supervision of a doctor. It is unlikely that you will be given too much or too little. However, tell your doctor or nurse if you have any concerns.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

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

Tell your doctor or nurse immediately if you 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. These may be signs of very rare severe allergic

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

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 'Instructions for use, disposal and other handling' below.
Incompatibilities have been reported between injectable forms of calcium folinate and injectable forms of droperidol, 5-fluorouracil, foscarnet and methotrexate.

Droperidol
- Droperidol 1.25 mg/0.5 ml with calcium folinate 5 mg/0.5 ml, immediate precipitation in direct admixture in syringe for 5 minutes at 25 °C followed by 8 minutes of centrifugation.
- Droperidol 2.5 mg/0.5 ml with calcium folinate 10 mg/0.5 ml, immediate precipitation when the medicines were injected sequentially into a Y-site without flushing the Y-side arm between injections.

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 glucose 50 mg/ml (5 %) solution for injection, 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.

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reaction (may affect up to 1 in 10,000 people). You may need urgent medical attention
- reddish flat, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis) (frequency cannot be estimated from the available data)

Uncommon (may affect up to 1 in 100 people)
- fever

Rare (may affect up to 1 in 1 000 people)
- insomnia
- agitation and depression (after high doses)
- an increase in convulsions (fits) in patients with epilepsy
- gastrointestinal disorders (after high doses)

Combination therapy with fluorouracil only
If you receive calcium folinate in combination with fluorouracil, it is more likely that you experience the following side effects:

Very common (may affect more than 1 in 10 people)
- bone marrow failure (including life-threatening conditions)
- inflammation of the lining of the intestine and mouth (life-threatening conditions have occurred)
- nausea, vomiting and diarrhoea (with monthly dosing)
- severe diarrhoea and dehydration (with weekly dosing)

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)
- elevated ammonia level in the blood

Tell your doctor if you experience diarrhoea or an inflammation of the lining of the mouth, as your doctor might wish to decrease the dose of fluorouracil until symptoms have fully disappeared.

Because diarrhoea may be a sign of toxicity to the stomach and gut, if you show these symptoms, you will be carefully monitored until the symptoms have disappeared completely. These symptoms may be the start of a rapid deterioration leading to death.

Your doctor may do tests to check for low levels of calcium in your blood.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via Yellow Card Scheme. Website: 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 Calcium folinate

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

Store in a refrigerator (2 °C – 8 °C). Keep the vial in the outer carton in order to protect from light.

<u>After opening the vial</u>: the product should be used immediately.

<u>Shelf life after dilution</u>
Chemical and physical in-use stability has been demonstrated for 4 days at 25 °C (protected from light) and at 2 to 8 °C after dilution with sodium chloride 9 mg/ml (0.9 %) solution for injection.
From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to the use are the responsibility of the user and would not normally be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8 °C after dilution with glucose 50 mg/ml (5 %) solution for injection.
From a microbiological point of view, unless the method of opening/dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

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 Calcium folinate contains
- The active substance is folinic acid as calcium folinate hydrate.

Each ml of solution contains calcium folinate hydrate equivalent to 10 mg folinic acid.
Each vial with 5 ml solution contains calcium folinate hydrate equivalent to 50 mg folinic acid.
Each vial with 10 ml solution contains calcium folinate hydrate equivalent to 100 mg folinic acid.
Each vial with 20 ml solution contains calcium folinate hydrate equivalent to 200 mg folinic acid.
Each vial with 30 ml solution contains calcium folinate hydrate equivalent to 300 mg folinic acid.
Each vial with 50 ml solution contains calcium folinate hydrate equivalent to 500 mg folinic acid.
Each vial with 100 ml solution contains calcium folinate hydrate equivalent to 1000 mg folinic acid.

Each 1 mg of folinic acid is equivalent to 1.08 mg of calcium folinate.

- The other ingredients are sodium chloride, sodium hydroxide (for pH adjustment), water for injections.

What Calcium folinate looks like and contents of the pack
Clear, colourless or yellowish solution free from visible particles.

5 ml, 10 ml, 20 ml, 30 ml, 50 ml or 100 ml of solution filled in clear glass vials closed with bromobutyl rubber stoppers sealed with aluminium flip-off seals. Vials are packed into outer cartons.

Pack sizes:
1, 5 or 10 vials of 5 ml
1 or 10 vials of 10 ml
1 or 10 vials of 20 ml
1 or 10 vials of 30 ml
1 or 10 vials of 50 ml
1 or 10 vials of 100 ml

Not all pack sizes may be marketed.

Marketing authorisation holder and Manufacturer
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Place for AS Kalceks internal code

Foscarnet
Foscarnet 24 mg/ml with calcium folinate 20 mg/ml; formation of a cloudy yellow solution reported.

Instructions for use, disposal and other handling
For single use only.
Use immediately after opening the vial. Discard any remaining contents after use.

The solution should be inspected visually prior to use. Do not use if there are any visible signs of deterioration (e.g. particles). Only clear solutions free from visible particles should be used.

<u>Dilution for intravenous infusion</u>
To administer the dose for a given patient, aseptically withdraw the appropriate amount of Calcium folinate 10 mg/ml solution for injection/infusion from the vial, then dilute it with any of compatible solutions mentioned below.
For storage conditions and shelf life after dilution, see section 5.

For intravenous infusion may be diluted with:
- sodium chloride 9 mg/ml (0.9 %) solution for injection;
- glucose 50 mg/ml (5 %) solution for injection.

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

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