PATIENT INFORMATION LEAFLET

CAFOLİNE 50 mg/5 mL I.M./I.V. Solution for Injection

Administered intravenously and intramuscularly.

Sterile

- ***Active Ingredient:*** Each 1 ml solution for injection contains 12.5 mg calcium folinate, equivalent to 10 mg folinic acid.
- ***Excipients:*** Sodium chloride, sodium hydroxide (pH adjuster), water for injection.

Before using this medicine, read all of this PATIENT INFORMATION LEAFLET carefully. Because, this leaflet includes important information for you.

- *Keep this patient information 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. Do not pass it on to others.*
- *During the use of this medicine, tell that you are using this medicine when you go to a doctor or hospital.*
- *Follow these instructions exactly as written. Do not use **higher or lower** dose other than your recommended dose.*

What is in this leaflet:

Headings are covered.

1. What CAFOLİNE is and what is it used for?

CAFOLİNE is an active metabolite of folic acid (vitamin) and plays a role in the synthesis of nucleic acids in our genes.

It is available in the form of a package containing 1 colorless vial (bottle) of 6 ml containing a clear solution of yellowish color.

CAFOLİNE is used to treat the following conditions:

- In the treatment of megaloblastic anemia (a special type of blood deficiency disease) in cases where folic acid deficiency cannot be replaced despite being taken orally.
- In children and adults, during cancer treatment or high doses of drugs such as methotrexate (a cancer drug), as well as to reduce or prevent the toxic effects of drugs such as trimethoprim (a type of antibiotic), pyrimethamine (a drug used to treat malaria), 5-fluorouracil (another cancer drug).

- It is used in cancer treatment together with 5-fluorouracil (another cancer drug).

2. What you need to know before you use CAFOLİNE?

CAFOLİNE should not be administered intrathecally into the spinal fluid.

If CAFOLİNE is to be administered together with methotrexate or 5-fluorouracil (cancer drugs), it should be administered by or under the strict supervision of a doctor specialized in cancer treatment.

DO NOT USE CAFOLİNE in below situations;

If;

- you are hypersensitive to the active substance (calcium folinate) or any of its other ingredients in CAFOLİNE solution for injection,
- if you have some kind of anemia (such as pernicious anemia) caused by vitamin B_{12} deficiency, do not use CAFOLİNE

USE CAFOLİNE CAREFULLY in below situations

If;

- you are using a medicine such as phenobarbital or phenytoin to treat epilepsy. It may be necessary to adjust the dose of your epilepsy medication.
- you use CAFOLİNE together with a drug called 5-fluorouracil for cancer treatment. you are also being treated with 5-fluorouracil and have an oral wound or inflammation of the oral mucosa, consult your doctor. This also applies if you have diarrhoea, which can be severe or life-threatening. your doctor may decide to reduce the dose or stop the treatment.
- you are using it together with a cancer medicine such as methotrexate,
- you are elderly or in poor general condition,
- you have decreased kidney function and are also being treated with methotrexate,
- you are pregnant or breastfeeding,

Calcium folinate treatment can mask pernicious anemia (a type of anemia) and other anemias caused by vitamin B12 deficiency.

If these warnings apply to you, even at any time in the past, please consult your doctor.

Use of CAFOLİNE with food and drink

There is no with interaction with food and drinks in terms of administration method.

Pregnancy

Consult your doctor or your pharmacist before using the drug.

Appropriate precautions should be taken to avoid becoming pregnant during CAFOLİNE treatment.

It is not known whether CAFOLİNE affects the fetus or reproductive capacity when given during pregnancy.

CAFOLİNE should not be used during pregnancy unless necessary.

During pregnancy, CAFOLİNE should be prescribed when the benefits to the mother outweigh the possible harmful effects on the fetus.

5-fluorouracil is generally not used during pregnancy; This also applies to the use of 5-fluorouracil together with calcium folinate.

During pregnancy, methotrexate should only be prescribed when its use is absolutely necessary and when the benefits to the mother outweigh the possible harmful effects on the fetus. In cases where treatment with methotrexate or other folic acid antagonists is carried out despite pregnancy or breast-feeding, there are no restrictions on the use of calcium folinate to reduce toxicity or prevent effects.

Also see the patient instructions for the medicinal products to be used together.

If you notice you are pregnant during treatment, consult your doctor or pharmacist immediately.

Lactation

Consult your doctor or your pharmacist before using the drug.

It is not known whether CAFOLİNE is excreted in breast milk. Your doctor will decide whether to stop breastfeeding or CAFOLİNE treatment.

Driving and using machines

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

Important information about some excipients in the content of CAFOLİNE

CAFOLİNE contains sodium chloride. This medicinal product contains more than 1 mmol (23 mg) sodium per dose; so it is essentially “sodium-free”.

Use with other medicines

- When used together with pyrimethamine, which is used to treat malaria, or trimethoprim, an antibiotic, sulfamethoxazole, it may reduce the effect of these drugs or completely neutralize them.
- When CAFOLİNE is given in high doses, it reduces the effects of epilepsy drugs such as phenobarbital and phenytoin and increases the frequency of convulsive seizures in

susceptible children.

– When used together with 5-fluorouracil, the effectiveness and harmful effects of tegafur and capecitabine, which are used in the treatment of cancer with fluorouracil, may be exacerbated.

– When an overdose of calcium folinate is taken following methotrexate administration, the effect of methotrexate treatment may decrease.

These warnings may also apply to medications used within a certain period of time before CAFOLİNE treatment is started or after it is stopped.

Never use any other medications unless recommended by your doctor.

If you are currently using any prescription or non-prescription medication of the following type or you have used it recently, please inform your doctor or pharmacist about them.

3. How to use CAFOLİNE?

• Instructions for appropriate use and dose/administration frequency:

Your doctor will determine the dose of your drug and administer it to you depending on your illness.

- Your doctor will make the necessary dosage adjustment for iatrogenic megaloblastic anemia (a special blood deficiency disease) that develops due to reasons such as a diet low in folic acid, frequent blood sampling, or frequent hemodialysis.

- If CAFOLİNE is given to you to prevent the harmful effects of an antifolinic drug (trimetrexate, trimethoprim, pyrimethamine, methotrexate), your doctor will adjust the dose of your drug according to the dose of the other drug you take.

- When used together with 5-fluorouracil, CAFOLİNE is given first and then 5-fluorouracil.Your doctor will determine how many cycles and how much CAFOLİNE and 5-fluorouracil you will receive.

• **Route and Method of administration:**

CAFOLİNE is intended for administration into a muscle (intramuscular) or into a vein (intravenous) and should be administered by persons experienced in administering such medications. It should not be administered into the spinal fluid (intrathecal). It should not be administered in the same syringe as other medications. For intravenous administration, no more than 160 mg of calcium folinate should be injected per minute due to the calcium content of the solution.

Use with methotrexate:
The recommended dose depends on your general health and the dose of methotrexate administered.

To reduce the side effects of methotrexate, calcium folinate is given 12-24 hours after the start of methotrexate administration. The initial calcium folinate dose is 15 mg (6-12 mg/m^2) and is repeated every 6 hours for 72 hours.

48 hours after the start of methotrexate administration, the amount of methotrexate in your body will be determined and the calcium folinate dose will be adjusted if necessary.

Concomitant use with the cancer drug 5-fluorouracil and as an antidote to the folic acid antagonists trimetrexate, trimethoprim and pyrimethamine:

For exact dosing instructions, see the "The following information is for healthcare personnel who will administer this medication" section at the end of this leaflet.

- **Various age groups:**

Use in Children:

High amounts of CAFOLİNE may reduce the effects of some epilepsy medications and cause an increase in the frequency of seizures in patients. There is insufficient data regarding the application in children and those under 18 years of age.

Use in Elderly:

Clinical data have shown that there are no significant differences in response to CAFOLİNE treatment between young and elderly patients. The risk of developing severe gastrointestinal toxicity is higher in elderly patients and patients in poor physical condition. Considering that the risk of renal impairment is higher in elderly patients, the dose should be adjusted more carefully and renal functions should be monitored.

Special use cases:

Renal failure:

Because this drug is excreted through the kidneys, the risk of toxic (damaging) reactions is higher in patients with renal impairment.
Since renal failure causes a delay in the excretion of methotrexate, if CAFOLİNE is used to prevent the harmful effects of methotrexate, it may be necessary to increase the dose of CAFOLİNE or extend the duration of administration.

Hepatic failure:

There is not enough information.

Talk to your doctor or pharmacist If you have an impression that the effect of CAFOLİNE strong or weak.

If you use more CAFOLİNE than you should:

Talk to a doctor or pharmacist if you have used more CAFOLİNE than you should use.

Overdose may cause possible allergic reactions and eliminate the chemotherapeutic effect of antifolinic drugs (folic acid antagonists such as methotrexate).

If you forget to use CAFOLİNE

Do not take a double dose to make up for forgotten doses.
Your doctor will decide when to administer the forgotten dose.

It is important to follow your doctor's instructions for the new administration of the next dose.

Effects that may occur when treatment with CAFOLİNE is terminated

Do not stop the treatment unless directed by your doctor.

If you have any further questions regarding the use of this product, ask your doctor or pharmacist.

4. What are the possible side effects?

Like all medicines, there may be side effects in people who are sensitive to the substances contained in CAFOLİNE.

If any of the following occur, stop using CAFOLİNE and IMMEDIATELY inform your doctor or go to the nearest hospital emergency department:

- Severe allergic reaction (effects that may develop as a result of allergy such as rash, swelling of hands, feet, ankles, face, lips, mouth or throat, feeling of fainting)

These are all very serious side effects.

If you have one of these, it means you have a serious allergy to CAFOLİNE.

You may need emergency medical attention or hospitalization.

All of these very serious side effects are very rare.

Side effects are listed below according to their frequency:

Very Common : Effects seen at least 1 in 10 patients
Common : Effects seen 1 to 10 in 100 patients
Uncommon : Effects seen 1 to 10 in 1,000 patients
Rare : Effects seen in less than one in 1,000 patients, but in more than one in 10,000 patients
Very Rare : Effects seen less than 1 in 10,000 patients
Unknown : Cannot be estimated from the available data

Uncommon side effects

- Fever

Rare side effects

- Insomnia, restlessness, depression after taking high doses
- Increased epilepsy seizures, cramps and/or fainting. Seizures have also been reported in people without epilepsy after taking high doses of calcium folinate.
- Gastrointestinal disorders after taking high doses

Very common side effects

- Serious allergic reactions - sudden itching and hives (redness) on your skin, swelling of your hands, feet, ankles, face, lips, mouth or throat (which may make it difficult to swallow or breathe) and feeling like you may faint.
- There have been cases where side effects, some of them fatal, have been observed (such as Stevens-Johnson syndrome and toxic epidermal necrolysis) when calcium folinate and other drugs associated with these side effects were used together. Symptoms of Stevens-Johnson syndrome include painful blisters in the mouth, throat, and genital area. Toxic epidermal necrolysis causes the skin to decompose. It is a life-threatening skin disease characterized by blistering and peeling of the skin. It is possible that calcium folinate may have a role affecting the outcome.

- Blood-related undesirable effects such as a decrease in the number of white blood cells (leukocytopenia) and a decrease in the number of platelets that help blood clot (thrombocytopenia) may also occur (including life-threatening conditions). Such undesirable effects are dose-related and their frequency can generally decrease by reducing the drug dose. These undesirable effects can be kept under control by closely monitoring blood values (white blood cells, platelets and electrolytes in the blood such as Na+, K+, Ca++ and creatinine values, which are an indicator of kidney function).

Concomitant use with 5-fluorouracil

Very common side effects

- Bone marrow failure
- Inflammation of the mucosa (secretion-producing tissue layer) in any part of the body (intra-oral wounds, inflammation of the oral mucosa, lip inflammation, pharynx inflammation, inflammation of the esophagus, inflammation of the last part of the large intestine including the anal tract) (life-threatening conditions have been reported)
- Vomiting and nausea (with monthly treatment)
- Severe diarrhea (with weekly treatment)
- Dehydration resulting from diarrhea may require hospitalization and may result in death (with weekly treatment).

Common side effects

- Skin disorders such as pain, swelling, itching and redness occurring on the hands and feet (palmar-plantar erythrodysesthesia)

Unknown

- Enzyme deficiency in urea synthesis (hyperammonemia)

Fatal events due to gastrointestinal toxicity (especially mucosal inflammation and diarrhea) and bone marrow suppression have been reported.

Reporting of side effects

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to

your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.
If you experience any side effect not mentioned in this patient information leaflet, inform your doctor or your pharmacist.

5. How to store CAFOLİNE?

Keep CAFOLİNE out of the reach and sight of children and within its packaging.

Store CAFOLİNE between 2-8ºC (in the refrigerator) in its original packaging, protected from light.

CAFOLİNE should be used immediately after dilution. If not used immediately, it can be stored at 2-8 ºC (in the refrigerator) for maximum 24 hours.

Use in compliance with the expiry date.

Do not use CAFOLİNE after the expiration date stated on the packaging.

Do not use CAFOLİNE if the product and / or packaging is not intact.

For single use. The microbiologically prepared infusion solution should be used immediately. If not used immediately, storage conditions of the ready-to-use solution prior to administration are the responsibility of the user and should generally not be stored in the refrigerator at 2-8ºC for more than 24 hours.

This medicine should be disposed of by healthcare personnel.

Do not throw away expired or unused drugs! Give it to the collection system determined by the Ministry of Environment, Urbanization and Climate Change.

Marketing Authorization Holder: Haver Trakya İlaç San. ve Tic. A.Ş.
Ulaş OSB Mah. D100 Cad. No:28/1, Ergene 2 OSB
Ergene/TEKİRDAĞ
Phone: (0282) 655 55 05

Manufacturing site ***:*** Haver Trakya İlaç San. ve Tic. A.Ş.
Ulaş OSB Mah. D100 Cad. No:28/1, Ergene 2 OSB
Ergene/TEKİRDAĞ
Phone: (0282) 655 55 05

This patient information leaflet was approved on 13/11/2023

THE FOLLOWING INFORMATION IS FOR THE HEALTHCARE PROFESSIONALS WHO ADMINISTER THIS MEDICINE

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

Preparation instructions:
CAFOLİNE should be visually inspected before use. Injection or infusion solutions should be clear and yellow in color. If a cloudy appearance or particles are observed, the solution should be discarded. Calcium folinate solution prepared for injection or infusion is for single use only. Unused and leftover solutions should be discarded.

CAFOLİNE is administered intramuscularly or intravenously (bolus or perfusion). When administered intravenously, doses of more than 160 mg per minute should not be given due to the calcium content of the solution.

To be administered as intravenous perfusion, CAFOLİNE can be reconstituted with 5% glucose or 0.9% sodium chloride.

IT MUST NOT BE ADMINISTERED INTRATECALLY.

As antidotes to folic acid antagonists trimetrexate, trimethoprim and pyrimethamine:

Trimetrexate toxicity:

Protection: Calcium folinate should be administered daily during trimetrexate treatment and until 72 hours after the last trimetrexate dose.
Calcium folinate is administered intravenously at a dose of 20 mg/m^2 every 6 hours with 5-10 minute infusions for a total of 80 mg/m^2, or orally at a dose of 20 mg/m^2 4 times a day at equal intervals.
Daily doses of calcium folinate should be adjusted depending on the hematological toxicity of trimetrexate.

Overdose (possibly occurring when calcium folinate is not administered with trimetrexate doses above 90 mg/m^2): After trimetrexate administration is discontinued, calcium folinate is given 40 mg/m^2 i.v. every 6 hours for 3 days.

Trimethoprim toxicity:
After trimethoprim administration is discontinued, 3-10 mg/day calcium folinate is administered until normal blood values are reached.

Pyrimethamine toxicity:
In high-dose or long-term low-dose pyrimethamine administration, 5-50 mg/day calcium folinate should be administered simultaneously, based on peripheral blood values.

In combination with 5-fluorouracil in cytotoxic therapy:
Different regimens and different doses are used, with no proven optimal dose. The following doses

are used to treat advanced or metastatic colorectal cancer in adults and the elderly and are provided as examples. There are no data on the use of this combination in children.

Twice a month regimen: CAFOLİNE is administered 200 mg/m^2 intravenous infusion lasting more than 2 hours, followed by 400 mg/m^2 bolus injection of 5-FU or 22-hour 5-FU (600 mg/m^2) infusion every two weeks for two consecutive days, on days 1 and 2. day.

Weekly regimen: CAFOLİNE is administered over 2 hours with 20 mg/m^2 iv bolus injection or 200-500 mg/m^2 iv infusion. CAFOLİNE is administered as an iv bolus injection of 500 mg/m^2 5-FU in the middle and at the end of the infusion.

Monthly regimen: CAFOLİNE is given by 20 mg/m^2 bolus injection or 200-500 mg/m^2 2-hour iv infusion followed by 425 or 370 mg/m^2 5-FU iv bolus injection for 5 consecutive days.

In combination therapy with 5-FU, modification of the 5-FU dose and treatment-free intervals may be necessary depending on the patient's health status, clinical response, and dose-limiting toxicity noted in the product information for 5-FU. No dose reduction of CAFOLİNE is necessary.

The number of repeat courses is at the discretion of the clinician.

Incompatibilities:
Incompatibility has been reported between the injectable form of calcium folinate and the injectable forms of droperidol, fluorouracil, foscarnet and methotrexate.

Droperidol:
When droperidol 1.25 mg/0.5 ml and 5 mg/0.5 ml calcium folinate are mixed directly in a syringe, precipitation forms in 5 minutes at 25°C, followed by 8 minutes of centrifugation to ensure complete precipitation.
When droperidol 2.5 mg/0.5 ml and 10 mg/0.5 ml calcium folinate are administered consecutively without purging the Y arm with air, immediate precipitation is observed in the Y arm.

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

A mixture of 1000 mg CAFOLİNE (100 mL of 10 mg/mL calcium folinate solution), 5000 mg 5-fluorouracil (100 mg to 50 mg/mL) and 40 ml saline was found to be stable for 48 hours under ambient conditions in infusion pumps (e.g. "Easy Pump" elastomeric infusion pump). Although there are no results regarding other mixtures, CAFOLİNE for injection/infusion should not be mixed with other drugs such as oxaliplatin or irinotecan.
Foscarnet:
It has been reported that it forms a cloudy yellow solution with foscarnet 24 mg/ml and calcium folinate 20 mg/ml.