PATIENT INFORMATION LEAFLET

CAFOLİNE 300 mg/30 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 300 mg/30 ml is an injectable solution whose active ingredient is calcium folinate.

Each 30 ml vial of CAFOLİNE contains 375 mg calcium folinate, equivalent to 300.00 mg folinic acid. It is yellow, clear solution. CAFOLİNE is presented in carton boxes of 1 vial.

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.
- To reduce or prevent the toxic effects of drugs such as methotrexate (a cancer drug) during cancer treatment or at high doses in children and adults

- 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,
- 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.
- you are using it together with a drug called 5-fluorouracil for cancer 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
- you are pregnant or breastfeeding

If these warnings are valid for you, even at any time in the past, please consult your doctor.

Use of CAFOLİNE with food and drink

CAFOLİNE has no interaction with food and drinks.

Pregnancy

Consult your doctor or your pharmacist before using the drug.

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.

If CAFOLİNE is to be used together with 5-fluorouracil, do not use it during pregnancy.
Do not use together with methotrexate.

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 contained in CAFOLİNE

CAFOLİNE contains sodium chloride. This medicinal product contains 4.36 mmol (100.26 mg) sodium in each dose (30 ml). This should be considered for patients on a controlled sodium diet.

Use with other medicines

- When used together with 5-fluorouracil, the effectiveness and harmful effects of fluorouracil may be intensified.
- 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.

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

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.

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 administration 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:

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.
Since CAFOLİNE is excreted through the kidneys, the risk of adverse effects may be increased in patients with renal impairment.

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 may eliminate the effect of antifolinic drugs (folic acid antagonists) or epilepsy drugs (antiepileptics).

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 100 in 1,000 patients
Rare	: Effects seen less than 1 in 1,000 patients
Very Rare	: Effects seen less than 1 in 10,000 patients

Very common side effects

- Severe nausea, vomiting, diarrhea, dehydration (especially observed when calcium folinate and 5-fluorouracil are used together)
- Severe effects, including oral sores, inflammation of the oral mucosa and lip inflammation, observed when calcium folinate and 5-fluorouracil are used together.

Uncommon side effects

- Fever

Rare side effects

- Insomnia, irritability, depression
- Increased epilepsy seizures, cramps and/or fainting
- Gastrointestinal disorders

Very rare side effects

- Allergic reactions including shock

Unknown

- Allergic reactions, hives
- Enzyme deficiency in urea synthesis (hyperammonemia) seen when calcium folinate and 5-fluorouracil are used together.
- Disorders in the hands and feet (Palmar-plantar erythrodysesthesia) seen when calcium folinate and 5-fluorouracil are used together.

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. It is possible that calcium folinate played a role in affecting the result.

If you experience any side effect not mentioned in this patient information leaflet, inform your doctor or your pharmacist.

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.

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.

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

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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 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.

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 1.25 mg/0.5 ml and 5 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.

Although there are no results regarding other mixtures, TANIV 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.