SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:

1 ml solution for injection contains 12.5 mg calcium folinate, equivalent to 10 mg folinic acid.

Excipients:

Sodium chloride…….8.50 mg/ml

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Vial containing solution for injection/infusion
Clear and yellow colored solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Neutralization of acute toxic effects of folic acid antagonists such as high doses (>100 mg/m^2) methotrexate, trimethoprim, pyrimethamine; It is indicated to reduce cytotoxicity when used together with 5-fluorouracil in the treatment of colorectal cancer and in the treatment of megaloblastic anemia due to folic acid deficiency in cases where folic acid cannot be replaced orally.

4.2. Posology and method of administration

Posology/frequency and duration of administration:

Administration of calcium folinate in methotrexate treatment:

Since the calcium folinate administration dosing regimen depends on whether high or medium doses of methotrexate are administered and its posology, the methotrexate protocol will determine the calcium folinate administration dosing regimen. Therefore, the best method is to adjust the dose and application method of CAFOLİNE according to whether methotrexate is administered at high or medium doses.

The following guide is an example of the dosing regimen used in adults, the elderly and children.

Calcium folinate administration should be done by parenteral administration in patients with other gastrointestinal disorders (vomiting, diarrhea, subileus, etc.) or malabsorption syndrome where enteral absorption cannot be assured. Doses above 25-50 mg/m^2 should be given parenterally due

to saturable enteral absorption of CAFOLİNE.

It is required for methotrexate doses exceeding 500 mg/m^2 (relative to body surface area) and should be considered for methotrexate doses of 100-500 mg/m^2 (relative to body surface area).

The dosage and duration of CAFOLİNE use depend on the dosage and type of methotrexate and/or the occurrence of toxicity symptoms and the individual excretion capacity of methotrexate.

As a rule, the first CAFOLİNE dose of 15 mg (6-12 mg/m^2) is given 12-24 hours after the start of the methotrexate infusion (not later than 24 hours).
The same dose is repeated every 6 hours for 72 hours. After several parenteral doses, oral administration can be started.

In addition to the administration of CAFOLİNE, measurements to ensure rapid excretion of methotrexate (maintenance of high urinary excretion and alkalinization of the urine) are integral parts of calcium folinate therapy. Renal functions should be monitored by measuring serum creatinine levels throughout the day.

The residual methotrexate level should be measured 48 hours after the start of methotrexate infusion.
If the residual methotrexate level is < 0.5 μmol/L, no additional dose is required.

If the residual methotrexate level is > 0.5 μmol/L, the CAFOLİNE dose should be adjusted according to the table below.

Residual methotrexate level in blood 48 hours after the start of methotrexate administration	Additional dose of CAFOLİNE to be administered every 6 hours for 48 hours or until methotrexate dose drops below 0.05 μmol/L
≥ 0.5 μmol / L	15 mg / m^2
≥ 1.0 μmol / L	100 mg / m^2
≥ 2.0 μmol / L	200 mg / m^2

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 500 mg/m^2 5-FU iv bolus injection 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.

In iatrogenic megaloblastic anemia:

Iatrogenic megaloblastic anemia may develop due to reasons such as a diet low in folic acid, frequent blood sampling, or frequent hemodialysis. 1 mg calcium folinate is given per day. There is no evidence that doses above 1 mg/day are more effective. Additionally, when the dose increases above 1 mg/day, urinary folate loss increases logarithmically. In patients with malabsorption syndrome or digestive disorders (vomiting, diarrhea), the parenteral route is preferred instead of oral route.

Method of Administration:

CAFOLİNE is administered intramuscularly or intravenously (bolus or infusion).

When administered intravenously, doses higher than 160 mg per minute should not be given due to the calcium content of the solution.

For intravenous infusion, calcium folinate should be diluted with 0.9% sodium chloride or 5% glucose solution before use. (see Section 6.6).

Additional information on special populations:

Renal impairment:

Renal impairment may cause delayed excretion of methotrexate. In this case, calcium folinate may need to be used in higher doses or the application may need to be extended. Because this drug is excreted through the kidneys, the risk of toxic reactions is higher in patients with renal impairment.

Since calcium folinate is excreted via the kidneys, the risk of adverse effects may be increased in patients with kidney disease (disorder).

Hepatic impairment:

There is not enough information.

Pediatric population:

Large amounts of calcium folinate may interfere with the effectiveness of some antiepileptic drugs and may increase the frequency of seizures in predisposed patients (see section 4.5).
There is insufficient data regarding application in children and adolescents.

Geriatric population:

Clinical data have shown no significant differences in response to calcium folinate therapy between young and elderly patients. The risk of severe gastrointestinal toxicity is greater in the elderly and people with debilitating diseases. Considering that the likelihood of renal impairment is also higher in elderly patients, more careful adjustment of dosage and monitoring of renal function is required.

4.3. Contraindications

- Those who are hypersensitive to CAFOLİNE or any of the ingredients contained in the drug,
- It should not be used in pernicious anemia or other anemias due to vitamin B_{12} deficiency. Although hematological symptoms regress, neurological symptoms may remain progressive.

For use during pregnancy and lactation when used in combination with calcium folinate, methotrexate or 5-fluorouracil, see section 4.6 Pregnancy and lactation and the summary of product characteristics for medicinal products containing methotrexate and 5-fluorouracil.

4.4. Special warnings and precautions for use

Calcium folinate should only be given by intramuscular or intravenous injection and should not be administered intrathecally. A case of death has been reported as a result of intrathecal calcium folinate administration following overdose of intrathecal methotrexate.

Calcium folinate should be used together with methotrexate or 5-fluorouracil only under the supervision of a physician experienced in administering chemotherapeutic agents used in the treatment of cancer.

Calcium folinate treatment may mask pernicious anemia and other anemias due to vitamin B_{12} deficiency.

Many cytotoxic drugs that directly or indirectly inhibit DNA synthesis cause macrocytosis (hydroxycarbamide, cytarabine, mercaptopurine, thioguanine). Such macrocytosis should not be treated with calcium folinate.

The patient should not become pregnant during treatment with CAFOLİNE. Patients should be informed about using contraceptive methods. If, despite these, pregnancy occurs, a strict risk-benefit analysis must be performed.

In epileptic patients treated with phenobarbital, phenytoin, pyrimidone and succinimides, there is a risk of an increased frequency of seizures due to a decrease in the plasma concentration of the antiepileptic drug. In clinical monitoring, it is recommended to adjust the antiepileptic drug dose when necessary, during CAFOLİNE administration and after discontinuation of treatment, while monitoring plasma concentrations (See Section 4.5).

CAFOLİNE / 5-fluorouracil combination:

CAFOLİNE; may increase the risk of toxicity of 5-fluorouracil, especially in the elderly or in patients with reduced physical performance. The most common symptoms are leukopenia, mucositis, stomatitis and/or diarrhea, which may be dose-limiting. When calcium folinate and 5-fluorouracil are used in combination, in case of toxicity, the 5-fluorouracil dose should be reduced more than the dose used alone.

In patients with symptoms of gastrointestinal toxicity, regardless of severity, 5-fluorouracil/CAFOLİNE combination therapy should not be initiated or continued until all symptoms have completely disappeared, and treatment should be discontinued until these symptoms disappear.

Because diarrhea may be a sign of gastrointestinal toxicity, patients with diarrhea should be carefully monitored until all symptoms have completely resolved. Because rapid clinical deterioration leading to death may occur. If diarrhea and/or stomatitis occur, it is appropriate to reduce the dose of 5-fluorouracil until the symptoms completely disappear. Especially elderly and patients with poor physical performance are prone to such toxicities due to their diseases. Therefore, special care should be taken when such patients are treated.

It is recommended to start with low dose 5-fluorouracil in elderly patients and patients receiving initial radiotherapy.

Calcium folinate should not be mixed with 5-fluorouracil in the same intravenous injection or

infusion.

Calcium levels should be monitored in patients receiving 5-fluorouracil/calcium folinate combination and additional calcium should be given if calcium levels are low.

CAFOLİNE / methotrexate combination:

For specific details on reducing methotrexate toxicity, see the methotrexate product summary.

Calcium folinate has no effect on non-hematological toxicities such as nephrotoxicity due to renal precipitation of methotrexate and/or its metabolites. Patients with early delayed elimination of methotrexate are at high risk of developing reversible renal failure and all toxicities associated with methotrexate (See Methotrexate Summary of Product Characteristics). Pre-existing or methotrexate-induced renal insufficiency may lead to delayed excretion of methotrexate and may require higher doses or longer periods of calcium folinate administration.

In particular, extremely high doses of calcium folinate should be avoided because excessive calcium folinate accumulation may occur after repeated methotrexate administration in central nervous system tumors. Because this may weaken the antitumor activity of methotrexate.

Since both medicinal products use the same transport system, resistance to methotrexate occurs as a result of decreased membrane transport, as well as resistance to calcium folinate.

Accidental overdose of a folic acid antagonist such as methotrexate should be treated urgently. As the time interval between methotrexate administration and calcium folinate administration increases, the effectiveness of calcium folinate in reducing toxicity decreases.

When abnormal laboratory findings or clinical toxicity are observed, the possibility of other drugs taken by the patient interacting with methotrexate (e.g. drugs affecting methotrexate excretion or binding to serum albumin) should be considered.

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

4.5. Interactions with other medicinal products and other forms of interaction

When calcium folinate is given together with a folic acid antagonist (such as co-trimoxazole, pyrimethamine), the effect of the folic acid antagonist may be reduced or completely eliminated.

Calcium folinate may increase the frequency of convulsive crises in susceptible patients by reducing the plasma concentrations and antiepileptic effects of antiepileptic drugs such as phenobarbital, phenytoin, primidone and succinimides (a decrease in the plasma levels of these drugs may be observed since folates, as one of the cofactors of hepatic metabolism, increase the hepatic metabolism of antiepileptic drugs) (See sections 4.4 and 4.8).

Calcium folinate administered concomitantly with 5-fluorouracil increases the efficacy and toxicity of 5-fluorouracil, tegafur and capecitabine (see sections 4.2, 4.4 and 4.8).

Additional information on special populations

Interaction studies with special populations have not been reported.

Pediatric population:

By reducing the antiepileptic effects of drugs such as phenobarbital, phenytoin and primidone, it may cause an increase in the frequency of seizures in susceptible children (See Sections 4.2 and 4.5).

4.6. Pregnancy and lactation

General advice

Pregnancy category: C

Women with childbearing potential / Contraception

There is no data indicating that CAFOLİNE has an effect on contraception methods.

Patients should be informed that they must use an appropriate contraceptive method during treatment with CAFOLİNE.

Pregnancy period

There is no sufficient data on the use of CAFOLİNE in pregnant women.

Animal studies are insufficient regarding effects on pregnancy /and-or/ embryonal/fetal development /and-or/birth /and-or/postnatal development (see section 5.3). The potential risk for humans is unknown.

CAFOLİNE should not be used during pregnancy unless necessary.

During pregnancy, methotrexate should only be prescribed when clearly indicated 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 lactation, there are no restrictions on the use of calcium folinate to reduce toxicity or prevent effects.

5-fluorouracil is generally contraindicated during pregnancy and lactation; This also applies to the combined use of 5-fluorouracil with calcium folinate.

Also see the summary of product characteristics of the medicinal products to be used in combination.

Lactation

It is not known whether calcium folinate is excreted in human breast milk. CAFOLİNE can be administered during breastfeeding when considered necessary according to therapeutic indications.

Reproductive ability / Fertility

It is not known whether calcium folinate affects reproductive ability.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Adverse reactions are listed below by system organ class and frequency: Very common (≥1/10); common (≥1/100 to < 1 /10); uncommon (≥1/1000 to <1/100); rare (≥1/10.000 to <1/1000); very rare (< 1/10.000); unknown (cannot be estimated from the available data.)

All therapeutic indications
Immune system diseases
Very Rare: Allergic reaction, including anaphylactic reactions and urticaria

Psychiatric diseases

Rare: Insomnia, restlessness, depression after high doses

Nervous system diseases

Rare: Increased frequency of epileptic attacks (See Section 4.5), convulsions and/or syncope

Seizures have been reported even in people without epilepsy after high doses of calcium folinate.

Gastrointestinal diseases

Rare: Gastrointestinal disorders after high doses

General disorders and diseases related to the administration site

Uncommon: Fever

There have been cases of side effects, some fatal, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), observed in patients using calcium folinate in combination with other medications associated with these complications. It is possible that calcium folinate played a role in affecting the result.

In addition, hematological undesirable effects such as leukocytopenia and thrombocytopenia may

occur. Such undesirable effects are dose-related and their frequency can generally decrease by reducing the dose of cytotoxic drug. These undesirable effects can be kept under control by closely monitoring hematological values (leukocyte, platelet, serum electrolytes such as Na+, K+, Ca++ and creatinine values).

Combination therapy with 5-fluorouracil

In general, the safety profile depends on the 5-fluorouracil dosage regimen applied due to the increase in 5-fluorouracil-induced toxicities. Additional undesirable effects in combination therapy with 5-fluorouracil are as follows:

Gastrointestinal diseases

Unknown: Hyperammonemia

Hepato-bilier diseases

Very Common: Bone marrow failure, including cases with fatal outcome.

Skin and subcutaneous tissue diseases

Very Common: Palmar-plantar erythrodysesthesia (hand-foot syndrome)

General disorders and diseases related to the administration site

Very Common: Mucositis (including stomatitis and scheelitis, pharyngitis, esophagitis, proctitis); Some deaths have occurred due to mucositis.

Monthly treatment:
Gastrointestinal diseases
Very Common: Vomiting and nausea
No increase in other toxicities (such as neurotoxicity) induced by 5-fluorouracil was observed.

Weekly treatment:

Gastrointestinal diseases

Very Common: Diarrhea and dehydration with high levels of toxicity may require hospitalization and may result in death.

Reporting of suspected adverse reactions

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.

4.9. Overdose and treatment

No sequelae have been reported in patients receiving higher than recommended doses of CAFOLİNE. However, excessive amounts of calcium folinate may destroy the chemotherapeutic effect of folic acid antagonists.

When overdose occurs with the combination of 5-fluorouracil and calcium folinate, the instructions regarding overdose of 5-fluorouracil should be followed.

5. PHARMACOLOGICAL PARTICULARS

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: Detoxifiers used in antineoplastic therapy
ATC Code: V03AF03

Calcium folinate is the calcium salt of 5-formyl-tetrahydrofolic acid (5-CH_3-THF). It is the active metabolite of folinic acid and an essential coenzyme for nucleic acid synthesis in cytotoxic therapy.

Calcium folinate is often used to reverse the effects of folate antagonists such as methotrexate and reduce toxicity.

It shares the same membrane transport carrier with calcium folinate and folate antagonists and competes with them for transport into the cell, stimulating the extracellular excretion of folate antagonists. They also protect cells from the effects of folate antagonists by replacing the decrease in the folate pool.

Calcium folinate acts as a pre-reduced source of H_4 folate. Therefore, it may prevent blockade by folate antagonists and be a source of various coenzyme forms of folic acid.

Calcium folinate is also used in the biochemical modulation of 5-FU to increase its cytotoxic activity. 5-FU exerts its effect by inhibiting thymidylate synthase (TS), the key enzyme involved in pyrimidine biosynthesis. Calcium folinate increases the TS inhibition effect of 5-FU by increasing the intracellular folate pool, stabilizing the 5-FU-TS complex and strengthening its activity.

As a result, intravenous calcium folinate is used in the treatment and prophylaxis of folate deficiency if improvement or protection cannot be achieved with oral folic acid administration. This can be used in severe malabsorption and during total parenteral nutrition. It is also used in the treatment of megaloblastic anemia due to folic acid deficiency when oral administration is not possible.

5.2. Pharmacokinetic properties

General Features

Absorption:

Systemic availability following intramuscular administration of the aqueous solution was comparable to intravenous administration, although lower peak plasma levels (C_{max}) were obtained.

Distribution:

The volume of distribution of calcium folinate is unknown.

Peak plasma levels of the parent substance (D/L-5-formyl-tetrahydrofolic acid, folinic acid) were achieved by i.v. It is reached 10 minutes after administration.

Following a 25 mg dose, the area under the curve (AUC) for L-5-formyl-THF and 5-methyl-THF are 28.4±3.5 mg min/l and 129±112 mg min/l, respectively. The inactive D-isomer is present in higher concentrations than L-5-formyl-tetrahydrofolate.

Biotransformation:

Calcium folinate is a racemic mixture and the L-form (L-5-formyl-tetrahydrofolate, L-5-formyl-THF) is the active enantiomer.

The major metabolic product of folinic acid is 5-methyl-tetrahydrofolic acid (5-methyl-THF), which occurs mainly in the liver and intestinal mucosa.

Elimination:

The elimination half-life of the active L-form is 32 – 35 minutes and the inactive D-form is 352-485 minutes.

The total terminal half-life of active metabolites is approximately 6 hours (intramuscular and intravenous administration).

Elimination is 80-90% with urine (5- and 10-formyl-tetrahydrofolate, inactive metabolites) and 5-8% with feces.

Linearity / nonlinearity:
No data available.

5.3. Pre-clinical safety data:

Apart from the information contained in other sections of this Summary of Product Characteristics, there is no preclinical information that can be considered relevant in terms of clinical safety.

6. PHARMACOLOGICAL PARTICULARS

6.1. List of excipients

Sodium chloride

Water for injection

6.2. 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 the syringe, precipitation forms in 5 minutes at 25ºC, followed by 8 minutes of centrifugation to ensure complete precipitation.
By applying droperidol 2.5 mg/0.5 mL and calcium folinate 10 mg/0.5 mL 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. 50 mg/ml fluorouracil and 20 mg/mL calcium folinate have been shown to be 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.

Infusion of 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 of saline in infusion pumps (e.g. "Easy Pump") was found to be stable for 48 hours under ambient conditions 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 to form a cloudy yellow solution with foscarnet 24 mg/mL and calcium folinate 20 mg/mL.

6.3. Shelf Life

24 months.
For single use.

6.4. Special precautions for storage

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

It is physically, chemically and microbiologically stable for 24 hours at 2-8°C in 5% Dextrose and 0.9% Sodium chloride solutions.

From a microbiological perspective, the product should be used immediately. If not used immediately, storage time and pre-use conditions are the responsibility of the user and should not be stored for longer than 24 hours at 2–8 ºC.

6.5. Nature and content of packaging

Clear, colorless 6 ml vial made of Type I glass closed with a gray bromobutyl rubber stopper and a flip-off aluminum cap.

6.6. Disposal of residues of the medicinal product for human use and other special measures

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

CAFOLİNE should be visually inspected before use.
Injection or infusion solutions should be clear yellowish 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 infusion). 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 an intravenous infusion, CAFOLİNE can be reconstituted with 5% glucose or 0.9% sodium chloride.

IT MUST NOT BE ADMINISTERED INTRATECALLY.

7. MARKETING AUTHORIZATION HOLDER

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8. 8. MARKETING AUTHORIZATION NUMBER

2019/354

9. DATE OF FIRST AUTHORIZATION / RENEWAL DATE OF AUTHORIZATION

First authorization date: 30.07.2019
Renewal date:

10. RENEWAL DATE OF SPC