SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF MEDICAL PRODUCT

KALSIFOSIN 300 mg/30 ml I.V./ I.M. Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug Substance:

1 ml of solution contains calcium folinate equivalent to 10 mg of folinic acid as active ingredient.

Excipient(s):

Sodium chloride …….….8,5 mg

Sodium hydroxide…..……... q.s.

See 6.1. for other excipients.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear, colorless-light yellow/yellow solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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

4.2. Posology and method of administration

Posology/Administration frequency and duration:

Calcium folinate rescue in methotrexate therapy:

Since the calcium folinate rescue dosage regimen depends heavily on the posology and method of the intermediate- or high-dose methotrexate administration, the methotrexate protocol will dictate the dosage regimen of calcium folinate rescue. Therefore, it is best to

refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of calcium folinate.

The following guidelines may serve as an illustration of regimens used in adults, elderly and children:

Calcium folinate rescue has to be performed by parenteral administration in patients with malabsorption syndromes or other gastrointestinal disorders where enteral absorption is not assured. Dosages above 25-50 mg/m^2 should be given parenterally due to saturable enteral absorption of calcium folinate.

Calcium folinate rescue is necessary when methotrexate is given at doses exceeding 500 mg/m^2 body surface and should be considered with doses of 100 mg – 500 mg/m^2 body surface.

Dosage and duration of calcium folinate rescue primarily depend on the type and dosage of methotrexate therapy, the occurrence of toxicity symptoms, and the individual excretion capacity for methotrexate.

As a rule, the first dose of calcium folinate is 15 mg (6-12 mg/m^2) to be given 12-24 hours (24 hours at the latest) after the beginning of methotrexate infusion.

The same dose is given every 6 hours throughout a period of 72 hours. After several parenteral doses treatment can be switched over to the oral form.

In addition to calcium folinate administration, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of the calcium folinate rescue treatment. Renal function should be monitored through daily measurements of serum creatinine.

Forty-eight hours after the start of the methotrexate infusion, the residual methotrexate-level should be measured.

If the residual methotrexate level is <0.5 micromol/l, no additional dose is required.

If the residual methotrexate-level is >0.5 µmol/l, calcium folinate dosages should be adapted according to the following table:

Residual methotrexate blood level 48 hours after the start of the methotrexate administration:	**Additional calcium folinate to be administered every 6 hours for 48 hours or until levels of methotrexate are lower than 0.05 µmol/l:**
≥0,5 µmol/l	15 mg/m^2
≥1 µmol/l	100 mg/m^2

≥2 µmol/l	200 mg/m^2

Antidote to the folic acid antagonists trimetrexate, trimethoprim, and pyrimethamine:
Trimetrexate toxicity:
Prevention: Calcium folinate should be administered every day during treatment with trimetrexate and for 72 hours after the last dose of trimetrexate.

Calcium folinate can be administered either by the intravenous route at a dose of 20 mg/m^2 for 5 to 10 minutes every 6 hours for a total daily dose of 80 mg/m^2 or by oral route with four doses of 20 mg/m^2 administered at equal time intervals. Daily doses of calcium folinate should be adjusted depending on the hematological toxicity of trimetrexate.

Overdosage (possibly occurring with trimetrexate doses above 90 mg/m^2 without concomitant administration of calcium folinate): after stopping trimetrexate, calcium folinate 40 mg/m^2 IV every 6 hours for 3 days.

Trimethoprim toxicity:
After stopping trimethoprim, 3-10 mg/day calcium folinate until recovery of a normal blood count.

Pyrimethamine toxicity:
In case of high dose pyrimethamine or prolonged treatment with low doses, calcium folinate 5 to 50 mg/day should be simultaneously administered, based on the results of the peripheral blood counts.

In combination with 5-fluorouracil in cytotoxic therapy:
Different regimens and different dosages are used, without any dosage having been proven to be the optimal one. The following regimens have been used in adults and elderly in the treatment of advanced or metastatic colorectal cancer and are given as examples. There are no data on the use of these combinations in children.

Bimonthly regimen: Calcium folinate 200 mg/m^2 by intravenous infusion over two hours, followed by bolus 400 mg/m^2 of 5-FU and 22-hour infusion of 5-FU (600 mg/m2) for 2 consecutive days, every 2 weeks on days 1 and 2.

Weekly regimen: Calcium folinate 20 mg/m^2 by bolus i.v. injection or 200 to 500 mg/m^2 as i.v. infusion over a period of 2 hours plus 500 mg/m^2 5-fluorouracil as i.v. bolus injection in the middle or at the end of the calcium folinate infusion.

Monthly regimen: Calcium folinate 20 mg/m^2 by bolus i.v. injection or 200 to 500 mg/m^2 as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m^2 5-fluorouracil as i.v. bolus injection during five consecutive days.

For the combination therapy with 5-fluorouracil, modification of the 5-fluorouracil dosage and the treatment-free interval may be necessary depending on patient condition, clinical response and dose limiting toxicity as stated in the product information of 5-fluorouracil. A reduction of calcium folinate dosage is not required.
The number of repeat cycles used is at the discretion of the clinician.

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

Method of administration:
Calcium folinate is administered intramuscularly or intravenously (bolus or infusion).
In the case of intravenous administration, no more than 160 mg of calcium folinate should be injected per minute due to the calcium content of the solution.
For intravenous infusion, calcium folinate may be diluted with 0.9% sodium chloride solution 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, it may be necessary to use higher doses of calcium folinate or to prolong the administration. Due to the

renal excretion of this drug, patients with renal impairment are at higher risk of toxic reactions.
Because calcium folinate is excreted by the kidneys, patients with kidney disease (disorder) may be at increased risk of undesirable effects.

Liver impairment:
There is no data.

Pediatric population:
Large amounts of calcium folinate may interfere with the efficacy of some antiepileptic drugs and may increase the frequency of seizures in predisposed patients (see section 4.5).
Data on practice in children and adolescents are insufficient.

Geriatric population:
Clinical data showed that there were 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 the debilitating disease. Given that elderly patients are also more likely to have renal impairment, more careful adjustment of dosage and monitoring of renal function is required.

4.3. Contraindications
• Known hypersensitivity to calcium folinate, or to any of the excipients.
• Pernicious anaemia or other anaemias due to vitamin B_{12} deficiency.
Regarding the use of calcium folinate with methotrexate or 5-fluorouracil during pregnancy and lactation, see section 4.6, “Pregnancy and Lactation” and the summaries of product characteristics for methotrexate- and 5-fluorouracil- containing medicinal products.

4.4. Special warnings and precautions for use
Calcium folinate should only be given by intramuscular or intravenous injection and must not be administered intrathecally. When folinic acid has been administered intrathecally following intrathecal overdose of methotrexate death has been reported.
Calcium folinate should be used with methotrexate or 5-fluorouracil only under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Calcium folinate treatment may mask pernicious anaemia and other anaemias resulting from vitamin B_{12} deficiency.
Many cytotoxic medicinal products – direct or indirect DNA synthesis inhibitors – lead to macrocytosis (hydroxycarbamide, cytarabine, mecaptopurine, thioguanine). Such macrocytosis should not be treated with folinic acid.

The patient should not become pregnant during treatment with calcium folinate. Patients should be informed about using contraceptive methods. If pregnancy does occur despite these, a rigorous risk-benefit analysis must be performed.
In epileptic patients treated with phenobarbital, phenytoin, primidone, and succinimides there is a risk to increase the frequency of seizures due to a decrease of plasma concentrations of anti-epileptic drugs. Clinical monitoring, possibly monitoring of the plasma concentrations and, if necessary, dose adaptation of the anti-epileptic drug during calcium folinate administration and after discontinuation is recommended (see section 4.5).

Calcium folinate/5-fluorouracil combination:
Calcium folinate may enhance the toxicity risk of 5-fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea, which may be dose limiting. When calcium folinate and 5-fluorouracil are used in combination, the 5- fluorouracil dosage has to be reduced more in cases of toxicity than when 5-fluorouracil is used alone.
Combined 5-fluorouracil/calcium folinate treatment should neither be initiated nor maintained in patients with symptoms of gastrointestinal toxicity, regardless of the severity, until all of these symptoms have completely disappeared.
Because diarrhoea may be a sign of gastrointestinal toxicity, patients presenting with diarrhoea must be carefully monitored until the symptoms have disappeared completely, since a rapid clinical deterioration leading to death can occur. If diarrhoea and/or stomatitis occur, it is advisable to reduce the dose of 5-FU until symptoms have fully disappeared. Especially the elderly and patients with low physical performance due to their illness are prone to these toxicities. Therefore, particular care should be taken when treating these patients.
In elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin with a reduced dosage of 5-fluorouracil. Calcium folinate must not be mixed with 5-fluorouracil in the same IV injection or infusion. Calcium levels should be

monitored in patients receiving combined 5-fluorouracil/calcium folinate treatment and calcium supplementation should be provided if calcium levels are low.

Calcium folinate/methotrexate combination:
For specific details on reduction of methotrexate toxicity refer to the SPC of methotrexate. Calcium folinate has no effect on non-haematological toxicities of methotrexate such as the nephrotoxicity resulting from methotrexate and/or metabolite precipitation in the kidney. Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure and all toxicities associated with methotrexate (please refer to the SPC for methotrexate). The presence of pre-existing- or methotrexate-induced renal insufficiency is potentially associated with delayed excretion of methotrexate and may increase the need for higher doses or more prolonged use of calcium folinate.
Excessive calcium folinate doses must be avoided since this might impair the antitumour activity of methotrexate, especially in central nervous system tumours where calcium folinate accumulates after repeated courses.
Resistance to methotrexate as a result of decreased membrane transport implies also resistance to folinic acid rescue as both medicinal products share the same transport system. An accidental overdose with a folate antagonist, such as methotrexate, should be treated as a medical emergency. As the time interval between methotrexate administration and calcium folinate rescue increases, calcium folinate effectiveness in counteracting toxicity decreases. The possibility that the patient is taking other medications that interact with methotrexate (eg, medications which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.

This medicinal product contains 255 mg of sodium chloride. This should be considered for patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction
When calcium folinate is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.
Calcium folinate may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed

because the hepatic metabolism is increased as folates are one of the cofactors) (see sections 4.4 and 4.8).
Concomitant administration of calcium folinate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil (see sections 4.2, 4.4 and 4.8).

Additional information on special populations:
There is no data on special populations.

Pediatric population:
May reduce the antiepileptic effects of drugs such as phenobarbital, phenytoin, primidone, resulting in an increased frequency of seizures in susceptible children (see sections 4.2 and 4.5).

4.6. Pregnancy and lactation
General recommendation
Pregnancy Category: C

Women who have childbearing potential/Birth control (Contraception)
There are no data on the effect of calcium folinate on contraceptive methods. Patients should be informed that they should use an appropriate contraceptive method during calcium folinate therapy.

Pregnancy
There are no adequate data from the use of calcium folinate in pregnant women.
Animal studies are insufficient for effects on pregnancy/and-or/embryonic/fetal development/and-or/partum/and-or/postnatal development (see section 5.3). The potential risk for humans is unknown.
Calcium folinate should not be used during pregnancy unless necessary.
During pregnancy, methotrexate should only be administered on strict indications, where the benefits of the drug to the mother should be weighed against possible hazards to the foetus. Should treatment with methotrexate or other folate antagonists take place despite pregnancy or lactation, there are no limitations as to the use of calcium folinate to diminish toxicity or counteract the effects.

5-fluorouracil use is generally contraindicated during pregnancy and contraindicated during breastfeeding; this applies also to the combined use of calcium folinate with 5-fluorouracil.
Please refer also to the summary of product characteristics for the medicinal products to be used in combination.

Lactation

It is not known whether calcium folinate is excreted into human breast milk. Calcium folinate can be used during breastfeeding when considered necessary according to the therapeutic indications.

Reproductive ability/Fertility

It is not known whether calcium folinate affects fertility.

4.7. Effects on ability to drive and use machines

There is no evidence that calcium folinate has an effect on the ability to drive or use machines.

4.8. Undesirable Effects

Evaluation of undesirable effects is based on the following frequencies:
Very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1.000 and < 1/100), rare (≥ 1/10.000 and < 1/1.000), very rare (< 1/10.000), not known (cannot be estimated from the available data).

All therapeutic indications

Immune system disorders

Very rare: Allergic reaction, including anaphylactic reactions and urticaria.

Psychiatric disorders

Rare: Insomnia, restlessness, depression after high doses

Nervous system disorders

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 disorders

Rare: Gastrointestinal disturbances after high doses

General disorders and administration site conditions

Uncommon: Fever

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

In addition, hematological undesirable effects such as leukocytopenia and thrombocytopenia may occur. Such undesirable effects are dose-related and their incidence may generally decrease with decreasing the dose of cytotoxic drug. These undesirable effects can be kept under control by closely monitoring hematological values (serum electrolytes such as leukocyte, thrombocyte, Na^+, K^+, Ca^{++} and creatinine values).

Combination therapy with 5-fluorouracil

In general, the safety profile is dependent on the 5-fluorouracil dosage regimen applied due to increased 5-fluorouracil-induced toxicities. Undesirable additional effects in combination therapy with 5-fluorouracil are as follows:

Gastrointestinal disorders

Not known: Hyperammonemia

Hepato-biliary disorders

Very common: Bone marrow deficiency, including cases with fatal outcomes.

Skin and subcutaneous tissue disorders

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

General disorders and administration site conditions

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

Monthly treatment:

Gastrointestinal disorders

Very common: Vomiting and nausea

No increase in other 5-fluorouracil-induced toxicities (such as neurotoxicity) was observed.

Weekly treatment:

Gastrointestinal disorders

Very common: Diarrhea and dehydration with a high degree of toxicity may require hospitalization and result in death.

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone: 0 800 314 00 08; fax: 0 312 218 35 99).

4.9. Overdose and Treatment

There have been no reported sequelae in patients who have received significantly more calcium folinate than the recommended dosage. However, excessive amounts of calcium folinate may nullify the chemotherapeutic effect of folic acid antagonists.

Should overdosage of the combination of 5-fluorouracil and calcium folinate occur, the overdosage instructions for 5-FU should be followed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment

ATC code: V03AF03

Calcium folinate is the calcium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and an essential coenzyme for nucleic acid synthesis in cytotoxic therapy. Calcium folinate is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as methotrexate.

Calcium folinate and folate antagonists share the same membrane transport carrier and compete for transport into cells, stimulating folate antagonist efflux. It also protects cells from

the effects of folate antagonist by repletion of the reduce folate pool. Calcium folinate serves as a pre-reduced source of H_4 folate; it can therefore bypass folate antagonist blockage and provide a source for the various coenzyme forms of folic acid.

Calcium folinate is also frequently used in the biochemical modulation of fluoropyridine (5-FU) to enhance its cytotoxic activity. 5-FU inhibits thymidylate synthase (TS), a key enzyme involved in pyrimidine biosynthesis, and calcium folinate enhances TS inhibition by increasing the intracellular folate pool, thus stabilising the 5FU-TS complex and increasing activity.

Finally, intravenous calcium folinate can be administered for the prevention and treatment of folate deficiency when it cannot be prevented or corrected by the administration of folic acid by the oral route. This may be the case during total parenteral nutrition and severe malabsorption disorders. It is also indicated for the treatment of megaloblastic anaemia due to folic acid deficiency, when oral administration is not feasible.

5.2. Pharmacokinetics Properties

General Features

Absorption:

Following intramuscular administration of the aqueous solution, systemic availability is comparable to an intravenous administration. However, lower peak serum levels (C_{max}) are achieved.

Distribution:

The distribution volume of folinic acid is not known.

Peak serum levels of the parent substance (D/L-5-formyl-tetrahydrofolic acid, folinic acid) are reached 10 minutes after i.v. administration.

AUC for L-5-formyl-THF and 5-methyl-THF were 28.4±3.5 mg.min/l and 129±112 mg.min/l after a dose of 25 mg. The inactive D-isomer is present in higher concentration than L-5-formyltetrahydrofolate.

Metabolism:

Calcium folinate is a racemate where 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 is predominantly produced in the liver and intestinal mucosa.

Elimination:

The elimination half-life is 32 - 35 minutes for the active L-form and 352 - 485 minutes for the inactive D-form, respectively. The total terminal half-life of the active metabolites is about 6 hours (after intravenous and intramuscular administration).

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

Linearity/Nonlinearity:

There is no data.

5.3. Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium Chloride

Sodium hydroxide and/or hydrochloric acid

Water for injection

6.2. Incompatibilities

Incompatibilities have been reported between injectable forms of calcium folinate and injectable forms of droperidol, 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 drugs were injected sequentially into a Y-site without flushing the Y-side arm between injections.

5-fluorouracil:

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.
No conclusions about other mixtures, although calcium folinate for injection/infusion should not be mixed with other drugs such as oxaliplatin or irinotecan.

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

6.3. Shelf life
24 months

6.4. Special precautions for storage
It is stored in the original box, protected from light, in the refrigerator between 2-8˚C.
Calcium folinate is stable in 5% glucose and 0.9% sodium chloride solution in light and at room temperature for 24 hours.
From a microbiological point of view, the product should be used immediately. If the solution has not been prepared in a controlled and aseptic environment, it should normally not be stored longer than 24 hours at 2–8ºC.

6.5. Nature and contents of container
KALSIFOSIN is offered for use with one 30 ml type I colorless glass vial and package leaflet.

6.6. Special precautions for disposal and other handling
Unused or waste substances must be disposed of in accordance with “Medical Waste Control Regulation” and “Packaging Waste Control Regulations”.

Preparation instructions
KALSIFOSIN should be visually inspected prior to use.
Solutions for injection or infusion should be clear, colorless to pale yellow/yellow.
If there is a cloudy appearance or particles are observed, the solution should be discarded. Calcium folinate solution for injection or infusion is for single use only. Unused and residual solutions should be discarded.

KALSIFOSIN is administered intramuscularly or intravenously (bolus or infusion). When administering intravenously, doses of more than 160 mg per minute should not be given due to the calcium content of the solution.
For administration as an intravenous infusion, KALSIFOSIN may be reconstituted with 5% glucose or 0.9% sodium chloride.
IT SHOULD NOT BE APPLIED INTRATHECALLY.

7. MARKETING AUTHORISATION HOLDER

VEM İlaç San. ve Tic. A.Ş.
Maslak Mahallesi AOS 55. Sokak
42 Maslak A Blok Sit. No: 2/134
Sarıyer/İSTANBUL/TURKEY

8. MARKETING AUTHORIZATION NUMBER(S)

2020/61

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORISATION

Date of first authorization: 31.03.2020
Date of renewal of the authorization:

10. DATE OF REVISION OF THE TEXT