הודעה על החמרה (מידע בטיחות) בעלון לרופא

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שם תכשיר באנגלית ומספר הרישום

LEUCOVORIN 10MG/ML

מספרי רישום 053 49 26932

שם בעל הרישום Salomon, Levin & Elstein Ltd, P.O.Box 3696, Petah Tikva 49133

טופס זה מיועד לפרוט החמרות בלבד

ההחמרות המבוקשות

טקסט חדש	טקסט נוכחי	פרק בעלון
- Known hypersensitivity to calcium folinate or to one of the excipients. - Pernicious anaemia or other anaemias as a result of a vitamin B_{12} deficiency. Concerning the use of calcium folinate and methotrexate or 5-fluorouracil during the pregnancy or during the period of lactation, see section 4.6 "Pregnancy and lactation" as well as the summary of product characteristics of methotrexate and 5-fluorouracil containing medicinal products.	- Known hypersensitivity to calcium folinate or to one of the excipients	**contraindications**
Only for intravenous or intramuscular administration. In 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 an intravenous infusion calcium folinate may be diluted before use with a 0.9% sodium chloride solution or with a 5% glucose solution. See also sections 6.3 and 6.6 ***Calcium folinate rescue with treatment of methotrexate:*** As the dosage schedule of the rescue treatment with calcium folinate is strongly dependent on the dose and the method of administration of methotrexate in intermediate or high dose, the methotrexate protocol will determine the dosage schedule of the rescue treatment with calcium folinate. It is therefore best to refer to the applied protocol of methotrexate to	*Calcium Leucovorin Rescue* A variety of dosage schedules of calcium leucovorin in combination with high-dose methotrexate have been used. In general, up to 120 mg are usually administered in divided doses, over 12-24 hours by intravenous infusion in 0.9% w/v Sodium Chloride Injection, followed by 12-15 mg intramuscularly, every 6 hours for the next 48 hours. In general, it is recommended that administration of leucovorin be consecutive, rather than simultaneous, with methotrexate administration so as not to interfere with methotrexate's antineoplastic effects. Usually, it should be administered within the first 26-42 hours of starting methotrexate infusion, in a dosage that will produce blood levels equal to or greater than	**Posology, dosage & administration**

intermediate or high dose for determining the dose and method of administration of calcium folinate. The following guidelines can serve as illustration for treatments used in adults, the elderly and children: Calcium folinate rescue should occur via parenteral administration in patients with malabsorption syndromes or other gastro-intestinal disorders in which the intestinal resorption is not guaranteed. Doses larger than 25-50 mg must be administered parenterally due to the saturatable intestinal resorption of calcium folinate. Calcium folinate rescue is needed if methotrexate is administered in doses of more than 500mg/m^2 of body surface and must be considered with doses of 100 mg - 500 mg/m^2 of body surface. The dose and the duration of the calcium folinate rescue is mainly dependent on the nature and the dose of the treatment of methotrexate, the occurrence of toxicity symptoms and the individual excretion capacity for methotrexate. Generally the first dose of calcium folinate is 15 mg (6-12 mg/m^2), administered 12 to 24 hours (at the latest 24 hours) after the start of the infusion of methotrexate. The same dose is administered every 6 hours for a period of 72 hours. After the administration of several parenteral doses can be switched to the oral form. In addition to the administration of calcium folinate measures for securing the rapid excretion of methotrexate (maintaining a high urine flow and alkalinisation of the urine) are an integral part of the calcium-folinate rescue treatment. The renal function must be followed through daily assessments of the serum creatinine. 48 hours after the initiation of the methotrexate infusion the residual concentration of methotrexate should be determined. If the residual concentration of methotrexate is greater than 0.5 µmol/l the doses of calcium folinate must be adjusted in accordance with the following table:	methotrexate blood levels. Where overdosage of methotrexate is suspected, the dose of calcium leucovorin should be administered within the first hour; it is usually ineffective after a delay of 4 hours. The duration of Leucovorin treatment varies with the dosage of methotrexate and varies in patients with renal function impairment or pleural or peritoneal effusions. The dose of leucovorin to counteract hematologic toxicity from folic acid antagonists with less affinity for mammalian dihydrofolate reductase than methotrexate (e.g. trimethoprim, pyrimethamine) is substantially less; 5-15 mg per day has been recommended. Give doses greater than 25 mg parenterally. Employ concomitant hydration (3 liters/day) and urinary alkalinization with sodium bicarbonate. Adjust the bicarbonate dose to maintain a urinary pH at 7 or greater. *Megaloblastic Anemia Secondary to Folate Deficiency* Give up to 1 mg daily. There is no evidence that I.M. doses greater than 1 mg/day have increased efficacy. In addition, the loss of folate in the urine increases as the amount administered exceeds 1 mg.	

Rest concentration of methotrexate in the blood 48 hours after the initiation of the administration of methotrexate:		Additional calcium folinate to be administered every 6 hours for 48 hours or until the concentration of methotrexate is lower than 0,05 µmol/l:	
≥ 0.5 µmol/l		15 mg/m²	
≥ 1.0 µmol/l		100 mg/m²	
≥ 2.0 µmol/l		200 mg/m²	

In combination with 5-fluorouracil for a cytotoxic treatment:
Various schedules and different doses were used, without a specific dosage appearing to be the optimal dose.
The following treatment schedules were used in adults and elderly patients for the treatment of advanced or metastasised colorectal cancer and are given as examples. There is no data available about the use of these combinations in children:

Two-weekly schedule: calcium folinate 200 mg/m² in intravenous infusion for 2 hours, followed by a bolus of 5-fluorouracil 400 mg/m² and an infusion of 5-fluorouracil (600 mg/m²) for 22 hours, on two consecutive days, every 2 weeks on days 1 and 2.

Weekly schedule: calcium folinate 20 mg/m² in intravenous bolus injection or 200 to 500 mg/m² in intravenous infusion for 2 hours, plus 500 mg/m² of 5-fluorouracil in intravenous bolus injection in the middle or at the end of the calcium folinate infusion.

Monthly schedule: calcium folinate 20 mg/m² in intravenous bolus injection or 200 to 500 mg/m² in intravenous infusion for 2 hours, immediately followed by 425 or 370 mg/m² of 5-fluorouracil in intravenous bolus injection for 5 consecutive days.

In combination therapy with 5-fluorouracil an adjustment of the 5-fluorouracil dose and of the treatment intervals may be necessary, depending on the condition of the patient, the clinical response and the dose- limiting toxicity as reported in the product characteristics of 5-fluorouracil. A reduction of the dose of calcium folinate is not required.
The number of repeat cycles must be determined by the physician

Antidote for the folic acid antagonists trimetrexate, trimethoprim and pyrimethamine: Toxicity of trimetrexate: - Prevention: calcium folinate must be administered every day during the treatment with trimetrexate and for 72 hours after the last dose of trimetrexate. Calcium folinate can be administered either intravenously in a dose of 20 mg/m^2 for 5 to 10 minutes every 6 hours up to a total daily dose of 80 mg/m^2, or orally with 4 doses of 20mg/m^2 administered at equal time intervals. The daily doses of calcium folinate must be adjusted on the basis of the haematological toxicity of trimetrexate - Overdose (possibly occurring with doses of trimetrexate above 90 mg/m^2 without concomitant administration of calcium folinate): after the discontinuation of trimetrexate, calcium folinate of 40 mg/m2 every 6 hours for 3 days. Toxicity of trimethoprim: - After the discontinuation of trimethoprim, 3-10 mg/day of calcium folinate until the recovery of a normal blood picture. Toxicity of pyrimethamine: - In cases of a high dose of pyrimethamine or a long-term treatment with low doses, 5 to 50 mg/day of calcium folinate must be administered concomitantly, depending on the results of the blood picture of the peripheral blood.		
Calcium folinate may only be injected intramuscularly or intravenously, and may not be administered intrathecally. Death was reported when folinic acid was administered intrathecally after an intrathecal overdose of methotrexate.	**Warnings** Calcium leucovorin is not recommended for use in the treatment of pernicious anemia or other megaloblastic anemias secondary to lack of vitamin B_{12}, since it may produce a hematologic remission while	**Special Warnings and Special Precautions for Use**

General Calcium folinate may only be used with methotrexate or 5-fluorouracil under the direct supervision of a clinician experienced in the use of chemotherapeutic products against cancer. A treatment with calcium folinate can mask a pernicious anaemia or other anaemias as a result of a vitamin B12 deficiency. Many cytotoxic medicinal products – direct or indirect inhibitors of the DNA synthesis – lead to macrocytosis (hydroxycarbamide, cytarabine, mercaptopurine, thioguanine). Such macrocytosis may not be treated with folinic acid. In epileptic patients, who are treated with phenobarbital, phenytoin, primidone and succinimides, the risk of an increased frequency of attacks exists due to a reduction of the plasma concentrations of the anti-epileptic products. Clinical monitoring, possibly monitoring of the plasma concentrations and, if needed, adjustment of the dose of the anti-epileptic product during the administration of calcium folinate and after the discontinuation, is recommended (see also section 4.5 “Interactions”). Calcium folinate / 5-fluorouracil Calcium folinate can potentiate the toxicity profile of 5-fluorouracil, especially in elderly or weakened patients. The most frequent symptoms are leukopenia, mucositis, stomatitis and/or diarrhoea, which can be dose limiting. If calcium folinate and 5-	neurologic manifestations continue to progress. In the treatment of accidental overdosages of folic acid antagonists, leucovorin should be administered as promptly as possible. As the time interval between antifolate administration (e.g., methotrexate) and leucovorin rescue increases, leucovorin's effectiveness in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin. When used as a rescue from the effects of methotrexate, calcium leucovorin should be used with caution in the presence of renal function impairment or pleural or peritoneal effusions, since such problems may affect the excretion of methotrexate. Patients receiving leucovorin as a rescue from the toxic effects of methotrexate should be under the supervision of a physician experienced in high-dose methotrexate therapy. Leucovorin enhances the toxicity of 5-fluorouracil. When these drugs are administered concurrently, the dosage of 5-fluorouracil must be lower than usually administered. Therapy with leucovorin/5-fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have completely resolved. Patients with diarrhea must be monitored with particular care until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. Elderly and/or debilitated patients were found to be at greater risk for severe gastrointestinal toxicity. Seizures and/or syncope have been reported rarely in cancer	

fluorouracil are used in combination, the dose of 5-fluorouracil, in case of toxicity, must be reduced more than if only 5-fluorouracil is used. A combination therapy of 5-fluorouracil / calcium folinate may not be started or continued in patients with symptoms of gastro-intestinal toxicity, regardless of the severity, until all these symptoms are completely resolved. Because diarrhoea can be a sign of gastro-intestinal toxicity, patients with diarrhoea must be carefully monitored until the symptoms have disappeared completely, because a rapid clinical decline, possibly lethal, can occur. If diarrhoea and/or stomatitis occur it is recommended to reduce the dose of 5-fluorouracil until the symptoms have disappeared completely. Especially elderly patients and patients with a low degree of physical functioning due to their illness are susceptible for this toxicity. For that reason extreme caution is needed for the treatment of these patients. It is recommended to start with a reduced dose of 5-fluorouracil in elderly patients and in patients who have undergone a preliminary radio-therapy. Calcium folinate may not be mixed with 5-fluorouracil in the same intravenous injection or infusion. The calcium concentrations must be followed in patients treated with the combination 5-fluorouracil /calcium folinate, and calcium supplements must be administered if the calcium concentrations are low. Calcium folinate / methotrexate See the SmPC of methotrexate for the	patients receiving leucovorin, usually in association with fluoropyrimidine (5-Fu) administration, and most commonly in those with CNS metastases or other predisposing factors, however, a causal relationship has not been established. **Precautions** Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the leucovorin. Leucovorin has no effect on non-hematologic toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney. The following checks are important in patient monitoring when leucovorin is used as rescue in high-dose methotrexate therapy: • Urine pH determinations: recommended prior to each dose of high-dose methotrexate therapy, and about every 6 hours throughout leucovorin rescue, until plasma or serum methotrexate concentrations are less than $5x10^{-8}$M, to ensure that pH remains greater than 7.0 so as to minimize the risk of methotrexate nephropathy from precipitation of methotrexate or metabolites in urine. • Creatinine clearance should be performed prior to initiation of high-dose methotrexate therapy. • Plasma methotrexate levels should be performed approximately 48 hours after methotrexate administration, to determine the duration of leucovorin treatment needed to maintain rescue. If levels	

specific details on the reduction of the toxicity of methotrexate. Calcium folinate does not have an effect on the non-haematological toxicity of methotrexate, like the nephrotoxicity as a result of methotrexate and/or a metabolic deposit in the kidneys. Reversible renal failure and all toxicities associated with methotrexate can occur in patients with a delayed premature elimination of methotrexate (see Module 1.3.1 of methotrexate). The presence of a pre-existing or by methotrexate induced renal insufficiency can involve a delayed excretion of methotrexate and may require higher doses or a more long-term use of calcium folinate. Excessive doses of calcium folinate must be avoided as this can reduce the anti-tumoral activity of methotrexate, especially in tumours of the central nervous system where calcium folinate accumulates after repeated administration. Resistance to methotrexate as a result of a reduced membrane transport also implies resistance against a rescue treatment with folinic acid, as both products make use of the same transport system. An accidental overdose with a folate antagonist like methotrexate must be treated like a medical emergency. As the time interval between the administration of methotrexate and the calcium folinate rescue becomes greater, the effect of calcium folinate to counteract the toxicity is reduced. The possibility that the patient takes other medicines that interact with methotrexate (for instance medicinal products that interfere with the elimination of methotrexate or its binding to	are too high, repeat monitoring every 24 hours until normal. • Daily serum creatinine determinations are recommended daily to detect developing renal dysfunction and to adjust dosage accordingly.	

serum albumin) should always be considered if abnormal laboratory values or clinical toxicity are observed. Each ml of solution contains 0.14 mmol (3.22 mg) sodium. This should be taken into account in patients on a controlled sodium diet		
If calcium folinate is administered in combination with a folic acid antagonist (for instance cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may be reduced or completely neutralised. Calcium folinate can reduce the effect of anti-epileptics like phenobarbital, primidone, phenytoin and succinimides and can increase the frequency of the attacks (a reduction of the plasma concentrations of enzyme inducing anti-convulsants can be observed because the liver metabolism is increased as folates are one of the co-factors)(see also sections 4.4 and 4.8).	***Leucovorin/Intrathecal Methotrexate:*** If methotrexate is administered intrathecally as local therapy during concurrent treatment with leucovorin, the antineoplastic effect of methotrexate may be negated by the presence of tetrahydrofolate, which diffuses readily into the cerebrospinal fluid (CSF). ***Leucovorin/Phenytoin/Primidone/P-aminosalicylic Acid/Sulfasalazine:*** An increase in seizure frequency and a decrease in serum phenytoin concentration to sub-therapeutic levels have been reported in patients receiving folic acid (particularly 15-20 mg/day) with phenytoin. Although this interaction has not been reported with leucovorin, it should be considered when using phenytoin and leucovorin concomitantly. The mechanism of phenytoin and folic acid interaction appears to be increased metabolic clearance of phenytoin and redistribution of phenytoin in the CSF and brain. Phenytoin and primidone are reported to cause a decrease in serum folate level, and may produce symptoms of folic acid deficiency in 27-91% of patients (but clinically important megaloblastic anemia in less than 1%) on long-term therapy. P-aminosalicylic acid and sulfasalazine may cause a similar deficiency. ***Leucovorin/Fluorouracil:*** Toxicity may be enhanced by leucovorin.	**Interaction with Other Medicaments and Other Forms of Interaction**

Both therapeutic indications: ***Immune system disorders*** *Very rare* Allergic reactions, including anaphylactoid/anaphylactic reactions and urticaria. ***Psychic disorders*** *Rare* Insomnia, agitation and depression after high doses. ***Gastro-intestinal system disorders*** *Rare* Gastro-intestinal complaints after high doses. ***Nervous system disorders*** *Rare* Increased frequency of attacks in epileptics (see also section 4.5 "Interactions with other medicinal products and other forms of interaction"). ***General disorders and administration site disorders*** *Uncommon* Fever has been reported after the administration of calcium folinate as a solution for injection. ***Combination therapy with 5-fluorouracil:*** The safety profile is generally dependent on the applicable administration schedule of 5-fluorouracil due to the increase of the toxicity induced by 5-fluorouracil. ***Metabolism and nutrition disorder*** *Not known* Hyperammonaemia ***Blood and lymphatic system disorders*** *Very common* Bone marrow failure, including fatal cases ***General disorders and administration site conditions*** *Very common* Mucositis, including stomatitis and cheilitis. Fatalities have occurred as a result of mucositis. ***Skin and subcutaneous tissue disorders*** *Common* Palmar-Plantar Erythrodysaesthesia Monthly schedule:	Adverse hypersensitivity reactions to calcium leucovorin are rare, but the following have been reported: pyrexia, hives, itching, rash, wheezing. Allergic sensitization including anaphylactoid reactions and urticaria has been reported.	**Adverse events**

Gastro-intestinal system disorders *Very common* Nausea and vomiting No increase of other toxicities induced by 5-fluorouracil (like neurotoxicity). Weekly schedule: ***Gastro-intestinal system disorders*** *Very common (more than 10%)* Diarrhoea with high degrees of toxicity, and dehydration, leading to hospitalisation for treatment and even death. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.		
Pregnancy No adequate and well-controlled clinical studies were performed in pregnant or breast-feeding women. No formal toxicity studies with calcium folinate were performed on the reproduction in animals. There are no indications that folic acid has toxic effects in case of administration during the pregnancy. During pregnancy methotrexate may only be administered in strict indications, whereby the benefit of the product for the mother must be weighed against the possible risks to the foetus. If a treatment with methotrexate or other folate antagonists takes place despite a pregnancy or breast-feeding, there are no limits on the use of calcium folinate to reduce the toxicity or counteract the effects. The use of 5-fluorouracil is generally contra-indicated during the pregnancy and is contra-indicated during the period of breast-feeding; this is also applicable for the combined use of calcium folinate and 5-fluorouracil. See also the Summary of	*Use in Pregnancy* Safety of use of this drug in pregnancy has not been established. Therefore, it should only be used if clearly needed, and when the potential benefits outweigh the unknown potential hazards to the fetus.	Pregnancy and lactation

Product Characteristics of medicinal products that contain methotrexate, other folate antagonists and 5-fluorouracil.		
No sequelae were reported in patients who had received significantly more calcium folinate than the recommended dose. Excessive amounts of calcium folinate can neutralise the chemotherapeutic effect of folic acid antagonists though. In case of an overdose of the combination 5-fluorouracil and calcium folinate, the guidelines for an overdose with 5-fluorouracil must be followed.	Excessive amounts of leucovorin may nullify the chemotherapeutic effect of folic acid antagonists.	Overdose