Package leaflet: Information for the patient
Leucovorin 10 mg/ml solution for injection/infusion*
Calcium folinate
PACKAGE LEAFLET: INFORMATION FOR THE USER

RX LEUCOVORIN 5mL Injection USP

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Leucovorin 10 mg/ml solution for injection/infusion*
Calcium folinate
Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Leucovorin is and what it is used for
Leucovorin is a detoxifying agent that is used with certain medicines for the treatment of cancer.
It is used
- in cancer treatment (cytotoxic therapy) as an antidote to reduce the toxicity (poisonousness) and effect of certain cancer drugs, the so-called folic acid antagonists (e.g. methotrexate). This purpose of doing so is to improve the tolerability of this cancer treatment, and it is referred to in medicine as “calcium folinate rescue”. In addition, Leucovorin is used in adults and children as an antidote in case of an overdose of these cancer drugs, to reduce or counter the signs of poisoning.
- in combination with the drug 5-fluorouracil in cancer treatment (cytotoxic therapy).

2. What you need to know before you use Leucovorin
Do not use Leucovorin:
- if you are allergic to calcium folinate or any of the other ingredients of this medicine (listed in section 6).
- in pernicious anaemia or other forms of megaloblastic anaemia caused by vitamin B12 deficiency. While improvements in blood count may occur, the nervous system signs continue to progress. This obscures the pernicious anaemia, making it more difficult for the doctor to detect it Please observe the directions on the use of Leucovorin in combination with methotrexate or 5-fluorouracil during pregnancy and while breast-feeding in section 2. Please also observe the package leaflets for medicines which contain methotrexate and other folic acid antagonists and 5-fluorouracil, if you are taking or using these.

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Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Leucovorin.
- If you suffer from a cancer of the central nervous system: Leucovorin may only be given as in injection into muscle (intramuscularly) or into a vein (intravenously) and must not be used in the central nervous system (intrathecally). Deaths have been reported after the intrathecal administration of folinic acid (the active substance of Leucovorin) following a prior intrathecal overdose of the cancer drug methotrexate.
- If you suffer from a cancer which is being treated with 5-fluorouracil (e.g. cancer of the bowel): While Leucovorin can be used together with 5-fluorouracil in cytotoxic cancer treatment, it has been shown that, when they are used at the same time, this increases the efficacy and toxicity of 5-fluorouracil (see also section 2 “Other medicines and Leucovorin”).
- If you suffer from epilepsy and are being treated for it: In epileptics who are being treated with the active substances phenobarbital, phenytoin, primidone and succinimides, there is a risk that the frequency of epileptic fits will increase, as Leucovorin reduces the concentration of these drugs in the blood. Clinical monitoring, if possible monitoring of the amount of active substance in the blood plasma (plasma level) and - if necessary - an adjustment of the dose of the epilepsy drug, are recommended during the use of calcium folinate (the active substance of Leucovorin) and after it is discontinued (see also section 2 “Other medicines and Leucovorin”).

General
Leucovorin should only be used together with the cancer drugs methotrexate or 5-fluorouracil under the direct supervision of a doctor who has experience with the use of chemotherapeutic agents in cancer.
Many medicines which are poisonous to the body’s cells (hydroxycarbamide, cytarabine, mercaptopurine, thioguanine) – direct or indirect inhibitors of the synthesis of the genetic substance DNA – lead to enlargement of the red blood cells (macrocytosis). This sort of macrocytosis should not be treated with Leucovorin.
Elderly and weakened patients
Since Leucovorin can increase the toxicity of 5-fluorouracil, the combination of these two drugs should only be used with particular care in elderly or weakened people, as these patients are at greater risk of developing poisoning in the gastrointestinal tract. For this reason, it may be necessary to reduce the dose of 5-fluorouracil. The most common signs that make such a reduction necessary are a low white blood cell count (leukopenia), inflammations of the mucous membranes (e.g. in the mouth or intestine) and/or diarrhoea.
Other medicines and Leucovorin
Tell your doctor, pharmacist or nurse if you are taking/using, have recently taken/used or might take/use any other medicines.
Leucovorin/5-fluorouracil
Leucovorin can increase the toxicity risk of 5-fluorouracil (a cell poison used in cancer treatment), particularly in elderly or weakened patients. The most common signs which may be dose-limiting are a reduction in the white blood cell count (leukopenia), inflammations of the mucous membranes and mucosa of the mouth (mucositis, stomatitis) and/or diarrhoea. If Leucovorin and 5-fluorouracil are used in combination, the 5-fluorouracil dose will need to be reduced to a greater extent at the onset of any signs of toxicity, than when 5-fluorouracil is given alone.

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In patients with signs of poisoning in the gastrointestinal tract (gastrointestinal toxicity, which is associated with diarrhoea or inflammation of the mucous membranes), regardless of its severity, the combination treatment with 5-fluorouracil and Leucovorin should neither be started nor continued until such a time as the patient no longer shows any symptoms. Since diarrhoea may be a sign of poisoning in the gastrointestinal tract (gastrointestinal toxicity), patients with diarrhoea must be carefully monitored until the patients no longer shows any symptoms, since a rapid deterioration, leading to death, may occur. If diarrhoea and/or stomatitis occur, it is advisable to reduce the 5-fluorouracil dose until the symptoms have resolved completely. Elderly people and patients who are in poor general health due to their disease are at a particularly high risk of developing these signs of poisoning. Special caution is therefore needed when treating these patients.
In elderly patients and patients who have had prior radiotherapy, the recommendation is to start with a reduced dose of 5-fluorouracil.
Leucovorin must not be mixed with 5-fluorouracil in the same intravenous injection or infusion.
Patients who are receiving combined 5-fluorouracil/Leucovorin treatment should have their calcium level monitored and should be given supplementary calcium if their calcium level is low.
Leucovorin/methotrexate
For specific details on reducing the toxicity of the cancer agent methotrexate, please refer to the package leaflet for methotrexate.
Leucovorin has no influence on methotrexate toxicity which does not affect the blood (nonhaematological toxicity), such as its toxicity against the kidneys (nephrotoxicity, as a consequence of methotrexate and/or the precipitation of the breakdown products of methotrexate in the kidneys).
Patients with delayed early excretion of methotrexate (methotrexate elimination) have a high likelihood of developing reversible kidney failure and all the signs of poisoning associated with methotrexate (please refer to the package leaflet for methotrexate). The presence of pre-existing or methotrexate-induced functional impairment of the kidneys (renal insufficiency) may be associated with the delayed excretion of methotrexate. This may necessitate higher doses or a more prolonged use of Leucovorin. Excessive amounts of Leucovorin must be avoided, as these can reduce the anti-tumour activity of methotrexate. This applies particularly to tumours of the central nervous system, in which the active substance of Leucovorin accumulates following repeated treatments.
Lack of sensitivity to methotrexate (methotrexate resistance) as a consequence of reduced transport through the membranes and into the cells also suggests lack of sensitivity to treatment with Leucovorin, as both medicines have the same transport mechanism.
An accidental overdose of a cancer drug such as methotrexate should be treated as a medical emergency. The longer the interval between the use of methotrexate and the administration of Leucovorin for calcium folinate rescue, the lower the efficacy of Leucovorin as a countermeasure to reduce the toxicity of the methotrexate.
The possibility that the patient is taking any other medication which interacts with methotrexate (e.g. medication which interacts with the elimination of methotrexate or its binding to serum albumin) should always be considered if abnormalities in laboratory values or clinical toxicity states are observed.
Leucovorin/other folic acid antagonists
If Leucovorin is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine), the efficacy of the folic acid antagonist may be reduced or cancelled out completely.

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Leucovorin/other medicines
Leucovorin may diminish the effects of medicines against epilepsy such as phenobarbital, primidone, phenytoin and succinimide, and thus lead to an increase in the frequency of epileptic fits (see also section 2 “Warnings and precautions” and section 4 “Possible side effects”).
Please note that this information may also apply to medicines that were used recently.
Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
What you need to know during pregnancy
a) When only Leucovorin is used (monotherapy):
There are no indications that the active substance of Leucovorin (calcium folinate) causes any harmful effects when it is given during pregnancy.
b) When Leucovorin is used together with other medicines:
During pregnancy, methotrexate (a drug used in cancer treatment) should only be used if found to be strictly indicated, after weighing up the benefit of the medicine for the mother against the potential risk to the foetus. Should treatment with methotrexate or other folic acid antagonists still be given despite a pregnancy or the fact that a mother is breast-feeding, there are no restrictions with respect to the use of Leucovorin to reduce the toxicity of methotrexate or to counter its effects.
In general, 5-fluorouracil must not be used during pregnancy or while breast-feeding. This also applies to the combined use of Leucovorin with 5-fluorouracil.
Please also observe the package leaflets for medicines which contain methotrexate and other folic acid antagonists and 5-fluorouracil, if you are taking or using them.
What you need to know while breast-feeding
It is not known whether the active substance of Leucovorin (calcium folinate) is passed into human breast milk. Calcium folinate may be used while breast-feeding, if this is deemed to be necessary within its therapeutic indications.
Driving and using machines
There are no indications that Leucovorin influences the ability to drive or use machines.
Leucovorin contains sodium
This medicine contains 0.13 mmol (3.03 mg) sodium per ml solution. You need to take this into account if you need to stay on a low-salt diet.

3. How to use Leucovorin
Leucovorin will be given to you by healthcare professionals. You can find detailed information on the dose and method of administration further below in this leaflet under “The following information is intended for doctors and healthcare professionals only”.
Method of administration
Leucovorin is administered into a vein (intravenously, i.v.) or into a muscle (intramuscularly, i.m.).
Dose
The doctor who is treating you or other healthcare professionals will give you Leucovorin. Your doctor will decide on the dose and frequency of administration. The healthcare staff will prepare the Leucovorin.

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Duration of use
The doctor who is treating you will decide on the duration of treatment.
If you have been given more Leucovorin than you should
There are as yet no reports about the consequences in patients who received significantly more than the recommended dose of Leucovorin. However, excessive amounts of Leucovorin may cancel out the chemotherapeutic effects of folic acid antagonists (e.g. methotrexate).
The directions on measures to be taken in an overdose of 5-fluorouracil should be followed in case of an overdose of the combination of 5-fluorouracil and Leucovorin.
If you forget to take Leucovorin
Inform your doctor or nurse immediately if you have received your cancer drug, but your Leucovorin was left out. Signs and symptoms of poisoning may develop if too little Leucovorin is administered during cancer therapy with methotrexate (see the section “The following information is intended for doctors and healthcare professionals only” further below in this leaflet).
Please tell your doctor of pharmacist if you feel that the effect of Leucovorin is too strong or too weak.
If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects have been observed:
Very rare: may affect up to 1 in 10,000 people
Severe allergic reaction - you may experience a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), and you may feel you are going to faint. This is a serious side effect. You may need urgent medical attention.
Nettle-rash (urticaria)
Uncommon: may affect up to 1 in 100 people
Fever
Rare: may affect up to 1 in 1,000 people
An increase convulsions (fits) in patients with epilepsy
Depression
Agitation
Problems with the digestive system
Difficulty sleeping (insomnia)

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Not known: frequency cannot be estimated from the available data
- Toxic Epidermal Necrolysis (TEN): A severe skin disorder including loss of the skin
- Steven-Johnson Syndrome (SJS): A severe skin disorder including blister shaped rash and inflammation of the skin, particularly on the hands and feet and around the mouth accompanied by fever

If you receive Leucovorin in combination with an anticancer medicine containing fluoropyrimidines, it is more likely that you experience the following side effects of this other medicine:
Very common: may affect more than 1 in 10 people
Nausea
Vomiting
Severe diarrhea
Drying out which may be due to diarrhea
Inflammation of the lining of the intestine and mouth (life-threatening conditions have occurred)
Reduction in the number of blood cells (including life-threatening conditions)
Common: may affect up to 1 in 10 people
Redness and swelling of the palms of the hands or the soles of the feet which may cause the skin to peel (hand-foot syndrome)
Not known: frequency cannot be estimated from the available data
Elevated ammonia level in the blood
Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. * By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Leucovorin
Storage conditions
Keep this medicine out of the sight and reach of children.
Store in a refrigerator (2 ºC to 8 ºC).
Store in the original packaging to protect the contents from light.
Do not use this medicine after the expiry date which is stated on the label and carton after “Expiry date” and “Exp.”, respectively. The expiry date refers to the last day of that month.
Shelf life after first opening or preparation
Leucovorin should be diluted immediately before use.
Leucovorin is intended for single use only.
After the container is first opened, any unused solution or remains of the solution for injection and infusion must be discarded.
Do not use this medicine if you notice clouding or particles are visible.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

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6. Contents of the pack and other information
What Leucovorin contains
The active substance is calcium folinate.
1 ml Leucovorin contains 10 mg folinic acid in the form of calcium folinate.
One ampoule with 1 (2, 3, 5) ml solution contains 10 (20, 30, 50) mg folinic acid in the form of calcium folinate. One injection vial with 10 (20, 25, 30, 50, 90, 100) ml solution contains 100 (200, 250, 300, 500, 900, 1000) mg folinic acid in the form of calcium folinate.
The other ingredients are: sodium chloride, sodium hydroxide, water for injections
What Leucovorin looks like and contents of the pack
Leucovorin is a clear, pale yellow to yellowish solution in a clear brown glass ampoule or injection vial.
Leucovorin is available in
- Ampoules of 1, 2, 3 and 5 ml
- Packs containing 1 ampoule, 5 ampoules and 10 ampoules
- Injection vials of 10, 20, 25, 30, 50, 90 and 100 ml
- Packs containing 1 injection vial, 5 injection vials and 10 injection vials

Not all pack sizes may be marketed.
Marketing Authorisation Holder
Manufactured in India by:
TAJ PHARMACEUTICALS LTD.
Mumbai, India
at SURVEY NO.188/1 TO 189/1,190/1 TO 4, ATHIYAWAD, DABHEL, DAMAN- 396210 (INDIA)

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The following information is intended for doctors and healthcare professionals only
Calcium folinate rescue in methotrexate therapy:
Since the calcium folinate rescue dosing regimen is highly dependent on the route and method of administration of the medium- or high-dose methotrexate treatment, it is the methotrexate protocol which determines the dosing regimen for the calcium folinate rescue. Therefore, when it comes to the route and method of administration of the calcium folinate, it is best to refer to the medium- or highdose methotrexate protocol that is being used.
The following guidelines may provide an illustration of the protocols used in adults, the elderly and children:
The administration of calcium folinate rescue by infusion or injection (parenteral administration) must be used in patients suffering from impaired nutrient uptake (malabsorption syndromes) or other gastrointestinal problems, if absorption in the gastrointestinal tract (enteral absorption) is uncertain.
Due to the saturable uptake of calcium folinate in the gastrointestinal tract (enteral absorption), doses of more than 25 to 50 mg should be administered parenterally.
Calcium folinate rescue becomes necessary when methotrexate is given at doses of more than 500 mg/m² body surface area, and should be considered at doses of 100 mg to 500 mg/m² body surface area.
The dosage and duration of the calcium folinate rescue depend primarily on the nature and dosage of the methotrexate therapy, the onset of the toxicity symptoms and the individual’s ability to excrete methotrexate (individual excretion capacity). As a guide, the first dose of calcium folinate, 15 mg (6 to 12 mg/m²), should be given 12 to 24 hours (no later than 24 hours) after the start of the methotrexate infusion. The same dose is administered every 6 hours over the next 72 hours. After several parenteral doses, the patient can be switched to the oral form.
In addition to the administration of calcium folinate, measures to ensure the prompt excretion of methotrexate (maintaining a high urine flow and alkalisation of the urine) are essential components of the calcium folinate rescue. Renal function should be monitored by means of daily serum creatinine determinations.
The remaining methotrexate level should be measured 48 hours after the start of the methotrexate infusion. If the remaining methotrexate level is > 0.5 µmol/l, the calcium folinate doses should be adjusted according to the following table:
Remaining blood level of methotrexate 48 hours after the start of methotrexate administration: Additional calcium folinate to be given every 6 hours for 48 hours, or until the methotrexate level 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 in cytotoxic therapy:
Various therapy protocols and doses are used, with no specific dose having been demonstrated as the optimum dose.
The following regimens are used in adults and the elderly for the treatment of advanced or metastatic colorectal carcinoma and are cited as examples. There are no data on the use of this combination in children:

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Two-monthly therapy protocol: calcium folinate at 200 mg/m² as an intravenous infusion over 2 hours, followed by 5-fluorouracil as a 400 mg/m2 bolus and a 22-hour infusion of 5-fluorouracil (600 mg/m2) on 2 consecutive days, every 2 weeks on days 1 and 2.
Weekly therapy protocol: calcium folinate 20 mg/m² as an i.v. bolus injection or 200 to 500 mg/m² as an i.v. infusion over 2 hours with 500 mg/m² 5-fluorouracil as an i.v. bolus injection in the middle or at the end of the calcium folinate infusion.
Monthly therapy protocol: calcium folinate at a dose of 20 mg/m² as an i.v. bolus injection or 200 to 500 mg/m² i.v. infusion over 2 hours, followed immediately by 5-fluorouracil at a dose of 425 or 370 mg/m² as an i.v. bolus injection on 5 consecutive days.
During the combination therapy with 5-fluorouracil, it may become necessary to adjust the 5-fluorouracil doses and the treatment intervals according to the patient’s condition, the clinical response and the dose-limiting toxicity, as specified in the product information on 5-fluorouracil.
A reduction of the calcium folinate dose is not necessary.
The number of repeat cycles is at the doctor’s discretion.
Antidote to the folic acid antagonists trimetrexate, trimethoprim and pyrimethamine:
Trimetrexate toxicity:
- Prevention:
Calcium folinate should be given daily during treatment with trimetrexate and during the 72 hours after the last trimetrexate dose. Calcium folinate may either be given intravenously at a dose of 20 mg/m² over 5 to 10 minutes, every 6 hours up to a total daily dose of 80 mg/m², or orally, divided into 4 doses of 20 mg/m² daily taken at uniform intervals. The daily calcium folinate doses should be adjusted according to the haematological toxicity of trimetrexate.
- Overdose (possibly occurring at trimetrexate doses of more than 90 mg/m² without accompanying calcium folinate administration): following the discontinuation of trimetrexate: administration of calcium folinate 40 mg/m² i.v. every 6 hours for 3 days.
Trimethoprim toxicity:
- Following the discontinuation of trimethoprim: administration of calcium folinate 3 to 10 mg/day until the blood count returns to normal.
Pyrimethamine toxicity:
- In case of high-dose pyrimethamine therapy or prolonged treatment at low doses, calcium folinate should be used concomitantly at 5 to 50 mg/day, based on the peripheral blood count results.
Method of administration:
Leucovorin 10 mg/ml solution may only be given into a vein (intravenously) or into a muscle (intramuscularly).
When given intravenously, an administration rate of 160 mg per minute should not be exceeded due to the calcium content.
The Leucovorin solution should be checked visually before use. The solution for injection or infusion should be a clear and yellowish solution. If any clouding or particles are observed, the solution should be discarded. Leucovorin solution for injection or infusion is intended for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.
Chemical intolerance has been reported between the injectable forms of calcium folinate and the injectable forms of droperidol, fluorouracil, foscarnet and methotrexate. Therefore, Leucovorin must not be mixed with medicinal products which contain these active substances.

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For intravenous infusion, calcium folinate may be diluted with 0.9% sodium chloride solution or 5% glucose solution before use (see also section 2 “Other medicines and Leucovorin”).
What you need to know if too little Leucovorin has been administered
When using Leucovorin to prevent the signs of intoxication resulting from methotrexate therapy, a dose that is too low is likely to be associated with appreciable toxic side effects on high-dose methotrexate pulse therapy (see package leaflet for medicinal products containing methotrexate).

RX LEUCOVORIN 5mL Injection USP

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