Package leaflet: Information for the user

Levofolinic acid 50 mg/ml solution for injection/infusion
Levofolinic acid

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.
- 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 Levofolinic acid is and what it is used for

Use of Levofolinic acid in combination with methotrexate
Levofolinic acid 50 mg/ml solution for injection/infusion belongs to the group of medicines called antidotes. These are substances which are used during cancer therapy (cytostatic therapy) to counteract the toxicity of cytostatics.

Levofolinic acid is used in cancer therapy in adults and children to diminish the toxicity and counteract the action of substances such as methotrexate which inhibit the action of endogenous folic acid (so called folic acid antagonists). An overdose of folic acid antagonists can be treated with Levofolinic acid as well.

Use of Levofolinic acid in combination with 5-fluorouracil
It has been shown that Levofolinic acid increases the action of certain cytostatics. Thus, it is also used in cancer therapy to increase the cell-damaging effects of an anticancer medicine called 5-fluorouracil.

2. What you need to know before you use Levofolinic acid

Do not use Levofolinic acid
- if you are allergic to levofolinic acid or any of the other ingredients of this medicine (listed in section 6).
- if you have pernicious anaemia or another anaemia due to vitamin B_{12} deficiency;
- in combination with 5-fluorouracil in case of existing contraindications against 5-fluorouracil, in particular when you are pregnant or breast-feeding;
- in combination with 5-fluorouracil if you have severe diarrhoea.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Levofolinic acid.

General
Levofolinic acid should only be used in combination with 5-fluorouracil or methotrexate under the direct supervision of a physician experienced in cancer therapy.

Levofolinic acid should not be administered into the spinal fluid (intrathecally) because severe side effects, including death, have been observed with this kind of treatment.

If you are administered certain cytotoxic (cell-damaging) substances such as hydroxycarbamide, cytarabine, mercaptopurin, thioguanine you may develop macrocytosis (enlarged red blood cells). Such macrocytosis should not be treated with levofolinic acid.

If you suffer from epilepsy which is treated with certain medicines (phenobarbital, phenytoin or primidone), there may be an increased risk of seizures. This results from a decrease of the concentration of antiepileptic substances in your blood plasma. Your doctor will probably carry out blood tests during the administration of levofolinic acid and after discontinuation. The concentration of your antiepileptic medicine in your blood plasma may be determined and, if necessary, the dose will be adapted.

Special precautions for the use of Levofolinic acid in combination with methotrexate
Your doctor will ensure that levofolinic acid is not given simultaneously with a folic acid antagonist (e.g. methotrexate), as the therapeutic effects of the antagonist may be reduced.

Your doctor will also avoid excessive levofolinic acid doses since this might impair the antitumour activity of methotrexate.

However, an accidental overdose of a folic acid antagonist such as methotrexate will be treated immediately as a medicinal emergency.

If you already suffer from impaired kidney function, inadequate hydration or if you use certain medicines against inflammation or pain (non steroidal anti-inflammatory agents e.g. ibuprofen, diclofenac or salicylates such as acetylsalicylate like aspirin) the excretion of methotrexate may be delayed by fluid accumulation, e.g. in the peritoneal cavity or in the space between thorax and lung. Under such circumstances, higher doses of Levofolinic acid or a prolonged administration period may be indicated.

Delayed excretion of methotrexate may in turn affect your kidney function which increases methotrexate blood levels.
In this case as well you may be given higher doses of Levofolinic acid or the administration period of levofolinic acid may be prolonged.

Special precautions for the use of Levofolinic acid in combination with 5-fluorouracil
In combined therapy with 5-fluorouracil, levofolinic acid may increase the risk of toxicity of 5-fluorouracil. The most common manifestations which may be dose limiting are:
- a reduced number of white blood cells,
- inflammation of the mucous membranes (e.g. in the mouth and/or stomach),
- diarrhoea.

If you suffer from watery stools two times per day and/or inflammation of the mucous membrane of the stomach (mild to moderate ulcers), you should consult your physician immediately.

You will neither be administered a combination therapy of 5-fluorouracil and levofolinic acid nor will a combination therapy be maintained if you show side effects affecting the gastrointestinal tract regardless of their severity.
In particular, if you develop diarrhoea the doctor will monitor you very carefully since your condition may deteriorate rapidly and severe side effects may occur. Your doctor will initiate or resume combination therapy of levofolinic acid and 5-fluorouracil after the gastrointestinal symptoms have completely disappeared.

Elderly or debilitated patients or patients who have undergone radiotherapy before should take special care as levofolinic acid may increase the risk of 5-fluorouracil toxicity.

Other medicines and Levofolinic acid
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The effect of one of the following medicinal products may be influenced if taken together with Levofolinic acid: phenobarbital, primidone, phenytoin, succinimide (medicines for treatment of epilepsy). Your doctor may check blood levels of these medicines and change your dose to prevent increased convulsions (fits).

If Levofolinic acid is given simultaneously with methotrexate it may stop this medicine from working properly.

Concomitant use of Levofolinic acid with 5-fluorouracil will increase effectiveness and side effects of 5-fluorouracil.

When Levofolinic acid is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine) the effectiveness of the folic acid antagonist may either be reduced or completely neutralised.

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 for advice before taking this medicine.
It is unlikely that your doctor will ask you to take/use a folic acid antagonist or 5-fluorouracil whilst you are pregnant or breast-feeding. However, if you have taken/used a folic acid antagonist whilst pregnant or breast-feeding, this medicine (Levofolinic acid) may be used to reduce its side effects.

Pregnancy
There are no indications that Levofolinic acid induces harmful effects if administered alone during pregnancy.

If you are pregnant, you should only be administered methotrexate if the benefits of your treatment outweigh the possible risks for your child.
If you are given methotrexate although you are pregnant, there are no limitations as to the use of disodium levofolinate to diminish or counteract the effects of methotrexate.

If you are pregnant you must not be administered a combination therapy with Levofolinic acid and 5-fluorouracil.

Breast-feeding
You must stop breast-feeding before treatment with methotrexate or 5-fluorouracil is started.

Levofolinic acid alone can be used during breast-feeding when considered necessary.

Driving and using machines
There is no evidence that Levofolinic acid alone affects the ability to drive or use machines. Your general condition is more significant than any effects induced by Levofolinic acid.

Levofolinic acid contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially “sodium-free”.

3. How to use Levofolinic acid

The preparation and administration of Levofolinic acid must only be carried out by trained healthcare professionals.

Levofolinic acid should always be administered into a vein, either undiluted by injection or by infusion after dilution.

Levofolinic acid must not be administered into the spinal fluid (intrathecally).

Levofolinic acid dose to prevent the manifestations of intoxication in methotrexate therapy
If you are administered a methotrexate dose of more than 500 mg/m² body surface in cancer therapy, you must also be administered levofolinic acid afterwards. With doses of 100 mg/m² – 500 mg/m² methotrexate your doctor may consider levofolinic acid administration.

Your doctor will ensure that the correct dose for your condition is given.

Levofolinic acid dose to increase the cytotoxic effects of 5-fluorouracil

There are different regimes for the combination therapy with Levofolinic acid and 5-fluorouracil (weekly regime, bimonthly regime and monthly regime).

Your doctor will ensure that the correct dose for your condition is given within the appropriate regime.

If you are given more Levofolinic acid than intended
Excessive amounts of Levofolinic acid may nullify the efficacy of folic acid antagonists such as methotrexate. Should overdose of the combination of 5-fluorouracil and Levofolinic acid occur, overdose instructions for 5-fluorouracil should be followed.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking Levofolinic acid and contact a doctor or go to your nearest emergency department immediately if you experience any of the following symptoms:

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.

Other side effects that may occur:

Uncommon (may affect up to 1 in 100 people):
- fever

Rare (may affect up to 1 in 1,000 people):
- difficulty sleeping (insomnia), agitation and depression after high doses
- problems with the digestive system (after high doses)
- increase in the frequency of convulsions (fits) in patients with epilepsy

Sodium levofolinate in combination with 5-fluorouracil:
If you receive levofolinic acid 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):
- reduction in the number of blood cells (including life-threatening conditions)
- inflammation (painful swelling and reddening) of the lining of the gut and mouth (life-threatening conditions have occurred)

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):
- higher than normal level of ammonia in the blood (a waste product the body makes)

Generally, the safety profile depends on the applied regimen of 5-fluorouracil due to enhancement of the 5-fluorouracil induced toxicities.

Monthly regimen:

Very common (may affect more than 1 in 10 people):
- vomiting, nausea

No enhancement of other 5-fluorouracil induced toxicities (e.g. neurotoxicity) was observed.

Weekly regimen:

- *Very common (may affect more than 1 in 10 people):*severe diarrhoea and drying out, which may be due to diarrhoea, resulting in hospital admission for treatment and even death

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible 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 Levofolinic acid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and the carton after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).

Keep the vial in the outer carton in order to protect from light.

6. Contents of the pack and other information

What Levofolinic acid contains
The active substance is levofolinic acid. Each ml of solution contains 54.65 mg disodium levofolinate, equivalent to 50 mg levofolinic acid.

Each 1 ml vial contains 54.65 mg disodium levofolinate, equivalent to 50 mg levofolinic acid.
Each 4 ml vial contains 218.6 mg disodium levofolinate, equivalent to 200 mg levofolinic acid.
Each 9 ml vial contains 491.85 mg disodium levofolinate, equivalent to 450 mg levofolinic acid.

The other ingredients are sodium hydroxide, hydrochloric acid, water for injections.

What Levofolinic acid looks like and contents of the pack

Levofolinic acid is a clear, colourless to slightly yellow solution for injection/infusion. It is marketed in colourless glass vials type I with bromobutyl rubber stoppers and aluminium flip-off caps.

Pack sizes:
Vials with 1 ml, 4 ml, or 9 ml solution for injection/infusion in packs of 1 or 5 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

This medicinal product is authorised in the member states of the EEA under the following names:

Belgium:	Levofolic 50 mg/ml solution injectable/pour perfusion Levofolic 50 mg/ml oplossing voor injectie / infusie Levofolic 50 mg/ml Injektions-/Infusionslösung
Denmark:	Levofolininsyre ”medac” 50 mg/ml injektions-/infusionsvæske, opløsning
Estonia:	Levofolinic acid medac 50 mg/ml süste-/infusioonilahus
Finland:	Levofolic 50 mg/ml injektio-/infuusioneste, liuos Levofolic 50 mg/ml injektions-/infusionsvätska, lösning
France:	Levofolinate de sodium medac 50 mg/ml, solution injectable/pour perfusion
Germany:	Levofolic 50 mg/ml Injektions-/Infusionslösung
Italy:	Sodio Levofolinato medac 50 mg/ml soluzione iniettabile o per infusione
Latvia:	Levofolic 50 mg/ml šķīdums injekcijai/infūzijai
Lithuania:	Levofolino rūgštis medac 50 mg/ml injekcinis ar infuzinis tirpalas
Norway:	Levofolinsyre medac 50 mg/ml injeksjons-/infusjonsvæske, oppløsning
Poland:	Levofolic 50 mg/ml roztwór do wstrzykiwań / do infuzji
Portugal:	Levofolic 50 mg/ml solução injetável ou para perfusão
Slovakia:	Levofolic 50 mg/ml injekčný/infúzny roztok
Slovenia:	Levofolic 50 mg/ml raztopina za injiciranje/infundiranje
Spain:	Ácido levofolínico medac 50 mg/ml solución inyectable y para perfusión
Sweden:	Natriumlevofolinat medac
United Kingdom:	Levofolinic acid 50 mg/ml solution for injection/infusion

This leaflet was last revised in 09/2023.

The following information is intended for healthcare professionals only:

Instructions for use and handling of Levofolinic acid

Preparation of solution for infusion must take place in aseptic conditions.

The solution for injection/infusion may be diluted with sodium chloride 9 mg/ml (0.9 %) solution or 5 % glucose solution.

Levofolinic acid is compatible with 5-fluorouracil.

Only clear solutions without visible particles should be used.

For single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

For intravenous use.

Shelf life after first opening or dilution

After mixing with 5-fluorouracil or dilution with sodium chloride 9 mg/ml (0.9 %) solution or 5 % glucose solution:

Chemical and physical in-use stability has been demonstrated for 72 hours at 20 – 25 °C.

From a microbiological point of view the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Posology and method of administration

Increasing the cytotoxicity of 5-fluorouracil

Different regimes and different doses are used, without any dose having been proven to be the optimal one.
The following regimes have been used in adults and elderly in the treatment of advanced or metastatic colorectal cancer and are given as examples.

Bimonthly regimen: 100 mg/m² levofolinic acid (= 109.3 mg/m² disodium levofolinate) by intravenous infusion over two hours, followed by bolus 400 mg/m² of 5-fluorouracil and 22-hour infusion of 5-fluorouracil (600 mg/m²) for 2 consecutive days, every 2 weeks on days l and 2.

Weekly regimen: 10 mg/m² levofolinic acid (= 10.93 mg/m² disodium levofolinate) by bolus injection or 100 to 250 mg/m² levofolinic acid (= 109.3 mg/m² to 273.25 mg/m² disodium levofolinate) as i.v. infusion over a period of 2 hours plus 500 mg/m² 5-fluorouracil as i.v. bolus injection in the middle or at the end of the disodium levofolinate infusion.

Monthly regimen: 10 mg/m² levofolinic acid (= 10.93 mg/m² disodium levofolinate) by bolus i.v. injection or 100 to 250 mg/m² levofolinic acid (= 109.3 mg/m² to 273.25 mg/m² disodium levofolinate) as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m² 5-fluorouracil as i.v. bolus injection during 5 consecutive days.

For the combination therapy with 5-fluorouracil, modification of the 5-fluorouracil dose 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 disodium levofolinate dose is not required.

The number of repeat cycles used is at the discretion of the clinician.

Paediatric population
No data on the use of these combinations are available.

Disodium levofolinate rescue in methotrexate therapy

Since the disodium levofolinate rescue dose regimen depends heavily on the posology and method of the intermediate- or high-dose methotrexate administration, the methotrexate protocol will dictate the dose regimen of disodium levofolinate rescue. Therefore, it is best to refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of disodium levofolinate.

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

Disodium levofolinate rescue has to be performed by parenteral administration in patients with malabsorption syndromes or other gastrointestinal disorders where enteral absorption is not assured. Doses above 12.5 – 25 mg levofolinic acid should be given parenterally due to saturable enteral absorption of disodium levofolinate.

Disodium levofolinate rescue is necessary when methotrexate is given at doses exceeding 500 mg/m² body surface and should be considered with doses of 100 mg – 500 mg/m² body surface.

Dose and duration of disodium levofolinate rescue primarily depend on the type and dose of methotrexate therapy, the occurrence of toxicity symptoms, and the individual excretion capacity for methotrexate. As a rule, the first dose of levofolinic acid is 7.5 mg (3 – 6 mg/m²) 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 levofolinic acid administration, measures to ensure the prompt excretion of methotrexate are important.

These measures include:

a. Alkalinisation of urine so that the urinary pH is greater than 7.0 before methotrexate infusion (to increase solubility of methotrexate and its metabolites).

b. Maintenance of urine output of 1800 – 2000 cc/m²/24 hr by increased oral or intravenous fluids on days 2, 3 and 4 following methotrexate therapy.

c. Plasma methotrexate concentration, BUN and creatinine should be measured on days 2, 3 and 4. These measures must be continued until the plasma methotrexate level is less than 10^{-7} molar (0.l μM).

Delayed methotrexate excretion may be seen in some patients. This may be caused by a third space accumulation (as seen in ascites or pleural effusion for example), renal insufficiency or inadequate hydration. Under such circumstances, higher doses of disodium levofolinate or prolonged administration may be indicated. Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure.

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 μmol/l, disodium levofolinate doses should be adapted according to the following table:

Residual methotrexate blood level 48 hours after the start of the methotrexate administration:	Additional levofolinic acid 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	7.5 mg/m²
≥ 1.0 µmol/l	50 mg/m²
≥ 2.0 µmol/l	100 mg/m²