Package leaflet: Information for the user
Levofolinic acid medac 50 mg/ml solution for injection or 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.
- 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.

What is in this leaflet:

1. What Levofolinic acid medac 50 mg/ml is and what it is used for

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

Levofolinic acid medac 50 mg/ml 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 medac 50 mg/ml as well.

Use of Levofolinic acid medac 50 mg/ml in combination with fluorouracil
It has been shown that Levofolinic acid medac 50 mg/ml 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 medac 50 mg/ml

Do not use Levofolinic acid medac 50 mg/ml
- 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 B12 deficiency,
- in combination with fluorouracil in case of existing contraindications against fluorouracil, in particular when you are pregnant or breast-feeding,
- in combination with fluorouracil if you have severe diarrhoea.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Levofolinic acid medac 50 mg/ml.

General
Levofolinic acid medac 50 mg/ml should only be used in combination with 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 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 drug substances (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 epileptic medication in your blood plasma may be determined and, if necessary, the dose will be adapted.

Special precautions for the use of Levofolinic acid medac 50 mg/ml 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 medac 50 mg/ml 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 medac 50 mg/ml or the administration period of levofolinic acid may be prolonged.

Special precautions for the use of Levofolinic acid medac 50 mg/ml in combination with fluorouracil
In combined therapy with fluorouracil, levofolinic acid may increase the risk of toxicity of 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 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 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 fluorouracil toxicity.

Other medicines and Levofolinic acid medac 50 mg/ml
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 medac 50 mg/ml: phenobarbital, primidone, phenytoin, succinimide (medicinal products for treatment of epilepsy).

If Levofolinic acid medac 50 mg/ml is given simultaneously with methotrexate it may stop this drug from working properly.

Concomittant use of Levofolinic acid medac 50 mg/ml with 5-Fluorouracil may increase the cytotoxic effect of 5-Fluorouracil.

When Levofolinic acid medac 50 mg/ml 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.

Pregnancy, breast-feeding and fertility

Pregnancy
There are no indications that Levofolinic acid medac 50 mg/ml 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 medac 50 mg/ml and fluorouracil.

Breast-feeding
You must stop breast-feeding before initiation of treatment with methotrexate or fluorouracil.

Levofolinic acid medac 50 mg/ml alone can be used during breast-feeding when considered necessary.

Driving and using machines
There is no evidence that Levofolinic acid medac 50 mg/ml alone affects the ability to drive or operate machines. Your general condition is more significant than any effects induced by Levofolinic acid medac 50 mg/ml.

3. How to use Levofolinic acid medac 50 mg/ml

The preparation and administration of Levofolinic acid medac 50 mg/ml must only be carried out by trained healthcare professionals.

Levofolinic acid medac 50 mg/ml Solution for injection or infusion should always be administered into a vein, either undiluted by injection or by infusion after dilution.

Levofolinic acid medac 50 mg/ml must not be administered into the spinal fluid (intrathecally).

Levofolinic acid medac 50 mg/ml dosage 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 medac 50 mg/ml dosage to increase the cytotoxic effects of fluorouracil

There are different regimes for the combination therapy with Levofolinic acid medac 50 mg/ml and 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 medac 50 mg/ml than intended
An accidental overdose of Levofolinic acid medac 50 mg/ml can decrease the efficacy of folic acid antagonists such as methotrexate. Should overdosage of the combination of fluorouracil and Levofolinic acid medac 50 mg/ml occur, overdosage instructions for fluorouracil should be followed.

4. Possible side effects

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

The following frequencies form the basis of the evaluation of side effects:

Very common: may affect more than 1 in 10 people
Common: may affect up to 1 in 10 people
Uncommon: may affect up to 1 in 100 people
Rare: may affect up to 1 in 1,000 people
Very rare: may affect up to 1 in 10,000 people
Not known: frequency cannot be estimated from the available data

Please tell your doctor immediately if you notice any side effects and discuss any further actions with him.

Uncommon	• General disorders (Fever)
Rare	• Psychiatric disorders (Insomnia, agitation and depression after high doses)
	• Gastrointestinal disorders (after high doses)

	• Nervous system disorders (increase in the frequency of attacks in epileptics)
Very rare	• Immune system disorders (allergic reactions including anaphylactoid reactions and urticaria)

Sodium levofolinate in combination with fluorouracil
Generally, the safety profile depends on the applied regimen of fluorouracil due to enhancement of the fluorouracil induced toxicities.

Monthly regimen

Very common	• Gastrointestinal disorders (vomiting, nausea) • General disorders (mucosal toxicities, which can be severe)

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

Weekly regimen

Very common	• Gastrointestinal disorders (diarrhoea with higher grades of toxicity, and dehydration resulting in hospital admission for treatment and even death)

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet.

5. How to store Levofolinic acid medac 50 mg/ml

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 medac 50 mg/ml 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 medac 50 mg/ml looks like and contents of the pack
Levofolinic acid medac 50 mg/ml is a clear, colourless to slightly yellow solution for injection or 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 or infusion in packs of 1 or 5 vials. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:
medac
Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstr. 3
20354 Hamburg
Germany

Manufacturer:
medac
Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstr. 3
20354 Hamburg
Germany

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

Belgium:	Levofolic 50 mg/ml solution injectable ou pour perfusion Levofolic 50 mg/ml oplossing voor injectie of infusie Levofolic 50 mg/ml Injektions- oder Infusionslösung
Czechia:	Levofolic 50 mg/ml injekční nebo infuzní roztok
Denmark:	Levofolininsyre ”medac” 50 mg/ml injektions- og infusionsvæske, opløsning
Estonia:	Levofolinic acid medac 50 mg/ml süste- või 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 ou pour perfusion
Germany:	Levofolic 50 mg/ml Injektions- oder Infusionslösung
Ireland:	Levofolinic acid medac 50 mg/ml Solution for injection or infusion
Italy:	Sodio Levofolinato medac 50 mg/ml soluzione iniettabile o per infusione
Latvia:	Levofolic 50 mg/ml šķīdums injekcijām vai infūzijām
Lithuania:	Levofolino rūgštis medac 50 mg/ml injekcinis/infuzinis tirpalas
Norway:	Levofolinsyre medac 50 mg/ml injeksjonsvæske/infusjonsvæske, oppløsning
Poland:	Levofolic 50 mg/ml roztwór do wstrzykiwań lub infuzji
Portugal:	Levofolic 50 mg/ml solução injectável ou para perfusão

Slovakia:	Levofolic 50 mg/ml injekčný alebo infúzny roztok
Slovenia:	Levofolic 50 mg/ml raztopina za injiciranje ali infundiranje
Spain:	Ácido levofolínico medac 50 mg/ml solución inyectable o para perfusión
Sweden:	Natriumlevofolinat medac, 50 mg/ml injektions- eller infusionsvätska, lösning
United Kingdom:	Levofolinic acid 50 mg/ml Solution for injection or infusion

This leaflet was last revised in 03/2013.

The following information is intended for healthcare professionals only:

Instructions for use and handling of Levofolinic acid medac 50 mg/ml

Preparation of the ready to use solution for infusion must take place in aseptic conditions.

Levofolinic acid medac 50 mg/ml Solution for injection or infusion may be diluted with 0.9 % sodium chloride solution or 5 % glucose solution.

Levofolinic acid medac 50 mg/ml is compatible with fluorouracil.

Only clear solutions without visible particles should be used.

For single use only; any unused product should be disposed of in accordance with local requirements.

For intravenous use.

Shelf life after first opening or dilution

After dilution with 0.9 % sodium chloride solution or 5 % glucose solution:

The in-use stability of the ready for use solution is 72 hours when stored at 20 – 25 °C.

However, from a microbiological point of view the product should be used immediately. If not used immediately, your doctor will ensure the correct in-use storage times and conditions prior to use in order to preserve the quality of the solution. Normally, this would be not longer than 24 hours at 2 °C – 8 °C, unless opening and preparation have taken place in controlled and sterile conditions.

Dosage and method of administration

<u>Increasing the cytotoxicity of fluorouracil</u>

Different regimes and different dosages are used, without any dosage 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.
There are no data on the use of these combinations in children.

<u>Bimonthly regimen</u>: 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 1 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 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 disodium levofolinate dosage is not required.

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

Disodium levofolinate rescue in methotrexate therapy

Since the disodium levofolinate 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 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. Dosages above 12.5 – 25 mg 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/m^2 body surface and should be considered with doses of 100 mg – 500 mg/m^2 body surface.

Dosage and duration of disodium levofolinate 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 levofolinic acid is 7.5 mg (3 – 6 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 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 (0.1 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 levofolinic acid 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 dosages 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