SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levofolinic acid 50 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion

Slightly yellow, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Disodium levofolinate is indicated

- to diminish the toxicity and counteract the action of folic acid antagonists such as methotrexate in cytotoxic therapy and overdose in adults and children;
- in combination with 5-fluorouracil in cytotoxic therapy.

4.2 Posology and method of administration

Posology

Disodium levofolinate in combination with 5-fluorouracil in cytotoxic therapy

The combined use of disodium levofolinate and 5-fluorouracil is reserved for physicians experienced in the combination of folinates with 5-fluorouracil in cytotoxic therapy.

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 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 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.

Disodium levofolinate can be safely mixed with 5-fluorouracil in a single infusion bag or pump without the risk of precipitation and catheter occlusion (see section 6.6). Combined infusion of disodium levofolinate and 5-fluorouracil can also be applied in treatment regimens containing oxaliplatin and/or irinotecan.

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 disodium levofolinate 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

Method of administration
Disodium levofolinate is administered intravenously, either undiluted by injection or by infusion after dilution. **Disodium levofolinate should not be administered intrathecally.**

Precautions to be taken before handling or administering the medicinal product
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Known hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Disodium levofolinate is not suitable for the treatment of pernicious anaemia or other anaemias due to vitamin B_{12} deficiency. Although haematological remissions may occur, the neurological manifestations remain progressive.

The combination of disodium levofolinate with 5-fluorouracil is not indicated in:
- existing contraindications against 5-fluorouracil
- severe diarrhoea.

Therapy with disodium levofolinate combined with 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 diarrhoea must be monitored with particular care until the diarrhoea has resolved, as rapid clinical deterioration leading to death can occur (see also sections 4.2, 4.4 and 4.5).

Regarding the use of disodium levofolinate with methotrexate or 5-fluorouracil during pregnancy and lactation, see section 4.6 and the summaries of product characteristics for methotrexate- and 5-fluorouracil-containing medicinal products.

4.4 Special warnings and precautions for use

Disodium levofolinate should only be given intravenously, either undiluted by injection or by infusion after dilution and must not be administered intrathecally.
When folinic acid has been administered intrathecally following intrathecal overdose of methotrexate, death has been reported.

General
Disodium levofolinate should be used with methotrexate or 5-fluorouracil only under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Disodium levofolinate 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, mercaptopurine, thioguanine). Such macrocytosis should not be treated with disodium levofolinate.

Epileptic patients
In epileptic patients treated with phenobarbital, phenytoin, primidone and succinimides there is a risk to increase the frequency of seizures due to decrease of plasma concentrations of anti-epileptic medicinal products. Clinical monitoring, possibly monitoring of the plasma concentrations and, if necessary, dose adaptation of the anti-epileptic medicinal product during disodium levofolinate administration and after discontinuation is recommended (see section 4.5)**.**

Disodium levofolinate/5-fluorouracil
In the combination regimen with 5-fluorouracil, the toxicity profile of 5-fluorouracil may be enhanced or shifted by disodium levofolinate, particularly in elderly or debilitated patients. The most common manifestations are leukopenia, mucositis, stomatitis and/or diarrhoea which may be dose limiting. When disodium levofolinate and 5-fluorouracil are used in combination, the 5-fluorouracil dose has to be reduced more in cases of toxicity than when 5-fluorouracil is used alone.

Gastrointestinal toxicities are observed more commonly and may be more severe or even life threatening (particularly stomatitis and diarrhoea). In severe cases, treatment is withdrawal of 5-fluorouracil and disodium levofolinate, and supportive intravenous therapy.
Combined 5-fluorouracil/disodium levofolinate 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-fluorouracil until symptoms have fully disappeared. Especially the elderly and patients with a low physical performance due to their illness are prone to these toxicities. Therefore, particular care should be taken when treating these patients.
Patients should be instructed to consult their treating physician immediately if stomatitis (mild to moderate ulcers) and/or diarrhoea (watery stools or bowel movements) two times per day occur (see also section 4.2).

Particular care should be taken in the treatment of elderly or debilitated patients or patients who have undergone preliminary radiotherapy, as these patients may be at increased risk of severe toxicity; in these patients it is recommended to begin with a reduced dose of 5-fluorouracil.

Disodium levofolinate/methotrexate
Disodium levofolinate should not be given simultaneously with an antineoplastic folic acid antagonist (e.g. methotrexate) to modify or abort clinical toxicity, as the therapeutic effect of the antagonist may be nullified except in the case of folic acid antagonist overdose (see below).
For specific details on reduction of methotrexate toxicity refer to the summary of product characteristics of methotrexate.

An accidental overdose with a folate antagonist, such as methotrexate, should be treated quickly as a medical emergency. As the time interval between methotrexate administration and disodium levofolinate rescue increases, disodium levofolinate effectiveness in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with disodium levofolinate. Delayed methotrexate excretion may be caused by third space fluid accumulation (i.e. ascites, pleural effusion), renal insufficiency, inadequate hydration or administration of non-steroidal anti-inflammatory drugs or salicylates. Under such circumstances, higher doses of disodium levofolinate or prolonged administration may be indicated.

Disodium levofolinate 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 summary of product characteristics 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 disodium levofolinate.

Excessive disodium levofolinate doses must be avoided since this might impair the antitumour activity of methotrexate, especially in CNS tumours where disodium 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.

The possibility that the patient is taking other medicinal products that interact with methotrexate (e.g., medicinal products which may interfere with methotrexate elimination or binding to serum albumin) should always be considered when laboratory abnormalities or clinical toxicities are observed.

Excipients with known effect:
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Disodium levofolinate is an antidote of folic acid antagonists – e.g. methotrexate. Following the use of methotrexate, disodium levofolinate overdose may lead to a loss of the effect of methotrexate therapy ("over-rescue").

When disodium levofolinate 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.

Concomitant administration of disodium levofolinate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil. Life-threatening diarrhoeas have been observed if 600 mg/m² of 5-fluorouracil (i.v. bolus once weekly) is given together with disodium levofolinate. When disodium levofolinate and 5-fluorouracil are used in combination, the 5-fluorouracil dose must be reduced more than when 5-fluorouracil is used alone (see sections 4.2, 4.4 and 4.8).

Disodium levofolinate 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 medicinal products may be observed because the hepatic metabolism is increased as folates are one of the cofactors) (see sections 4.4 and 4.8)**.**

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. No formal animal reproductive toxicity studies with disodium levofolinate have been conducted. There are no indications that folinic acid induces harmful effects if administered during pregnancy. During pregnancy, methotrexate should only be administered on strict indications, where the benefits of the medicinal product to the mother should be weighed against possible hazards to the foetus. Should treatment with methotrexate or other folate antagonists take place despite pregnancy, there are no limitations as to the use of disodium levofolinate to diminish toxicity or counteract the effects.

5-fluorouracil use is generally contraindicated during pregnancy and breast-feeding; this applies also to the combined use of disodium levofolinate with 5-fluorouracil.

Please refer also to the summaries of product characteristics for methotrexate-, other folate antagonists and 5-fluorouracil-containing medicinal products.

Breast-feeding
It is not known whether disodium levofolinate is excreted into human milk. Disodium levofolinate alone can be used during breast feeding when considered necessary according to the therapeutic indications.
However, methotrexate or 5-fluorouracil are excreted in human milk, and both active substances are contraindicated during breast-feeding. Breast-feeding must be discontinued before such treatment is initiated.

Fertility
No information is available on the effects of folinic acid alone on fertility and general reproductive performance.

4.7 Effects on ability to drive and use machines

Disodium levofolinate has no or negligible influence on the ability to drive and use machines. The general condition of the patient is likely to be more significant than any effects induced by this medicinal product.

4.8 Undesirable effects

Frequencies
- Very common (≥1/10)
- Common (≥1/100 to <1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <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 reactions including anaphylactoid / anaphylactic reactions and urticaria
Psychiatric disorders	Rare Insomnia, agitation and depression after high doses
Nervous system disorders	Rare Increase in the frequency of attacks in epileptics (see also section 4.5)
Gastrointestinal disorders	Rare Gastrointestinal disorders after high doses
General disorders and administration site conditions	Uncommon Fever has been observed after administration of disodium levofolinate as solution for injection

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

Blood and lymphatic system disorders	Very common Bone marrow failure, including fatal cases
Metabolism and nutrition disorders	Not known Hyperammonaemia
Skin and subcutaneous tissue disorders	Common Palmar-plantar erythrodysaesthesia
General disorders and administration site conditions	Very common Mucositis, including stomatitis and cheilitis. Fatalities have occurred as a result of mucositis.

Monthly regimen:

Gastrointestinal disorders	Very common Vomiting and nausea

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

Weekly regimen:

Gastrointestinal disorders	Very common Diarrhoea with higher grades of toxicity, and dehydration resulting in hospital admission 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.

4.9 Overdose

There have been no reported sequelae in patients who have received significantly more disodium levofolinate than the recommended dose.
There is no specific antidote.

When using methotrexate, an overdose of disodium levofolinate may result in a decrease of efficacy of methotrexate ("over-rescue").

Should overdose of the combination of 5-fluorouracil and disodium levofolinate occur, overdose instructions for 5-fluorouracil should be followed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment, ATC code: V03AF10

Mechanism of action
Folinic acid is the formyl derivative of tetrahydrofolic acid i.e. the active form of folic acid. Levofolinic acid is the biologically active l-isomer of racemic folinic acid. It is involved in various metabolic processes including purine synthesis, pyrimidine nucleotide synthesis and amino acid metabolism.

Pharmacodynamic effects
Biochemical rationale for the methotrexate rescue therapy with disodium levofolinate
Levofolinic acid is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as methotrexate. Levofolinic acid 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 reduced folate pool. Levofolinic acid does not require reduction by the enzyme dihydrofolate reductase. Thus it serves as a pre-reduced source of H4 folate; it can therefore bypass folate antagonist blockage of the dihydrofolate reductase and provide a source for the various coenzyme forms of folic acid.

Biochemical rationale for the combination of disodium levofolinate with 5-fluorouracil:
5-fluorouracil can inhibit DNA synthesis by binding to the enzyme thymidylate synthetase. The combination of disodium levofolinate with 5-fluorouracil results in the formation of a stable ternary complex consisting of thymidylate synthetase, 5-fluorodeoxy-uridinemonophosphate and 5,10-methylenetetrahydrofolate. This leads to an extended blockade of thymidylate synthetase with enhanced inhibition of DNA biosynthesis, resulting in increased cytotoxicity as compared to 5-fluorouracil monotherapy.

5.2 Pharmacokinetic properties

Disodium levofolinate is bioequivalent with calcium levofolinate as well as with the racemate disodium folinate with respect to plasma concentrations of levofolinic acid and the main, active metabolite, 5-methyltetrahydrofolic acid after intravenous administration of the same molar dose of the active isomer.

Distribution
The protein binding of levofolinic acid is about 27 %. The volume of distribution is about 17.5 litres.

Biotransformation
The active isomeric form levofolinic acid (l-5-formyltetrahydrofolic acid) is quickly metabolised to 5-methyltetrahydrofolic acid in the liver. It is assumed that this conversion is not linked to the presence of dihydrofolate reductase.

Elimination
About 20 % of an intravenous dose is excreted as unchanged levofolinic acid in urine. The clearance for levofolinic acid is about 205 ml/min. After intravenous administration, the half-life of levofolinic acid and the active metabolite, 5-methyltetrahydrofolic acid, is 0.5 hours and 6.5 hours, respectively.

5.3 Preclinical safety data

Toxicity tests on combined use with 5-fluorouracil have not been carried out.
No further information is available of relevance to the prescriber which is not already included in other relevant sections of the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

After mixing with 5-fluorouracil or dilution with sodium chloride 9 mg/ml (0.9 %) solution or 5 % glucose solution (see section 6.6):
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 8 °C unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

Levofolinic acid is administered intravenously, either undiluted by injection or by infusion after dilution. 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische
Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: {DD month YYYY}
Date of latest renewal: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

10/2025