SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sodiofolin 50 mg/ml, solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodiofolin contains 54.65 mg/ml disodium folinate equivalent to 50 mg/ml folinic acid.

2 ml of solution contains 109.3 mg disodium folinate equivalent to 100 mg folinic acid.
4 ml of solution contains 218.6 mg disodium folinate equivalent to 200 mg folinic acid.
6 ml of solution contains 327.9 mg disodium folinate equivalent to 300 mg folinic acid.
8 ml of solution contains 437.2 mg disodium folinate equivalent to 400 mg folinic acid.
10 ml of solution contains 546.5 mg disodium folinate equivalent to 500 mg folinic acid.
18 ml of solution contains 983.7 mg disodium folinate equivalent to 900 mg folinic acid.

Excipient(s) with known effect
Sodium

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 folinate 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 cytotoxic therapy, the procedure is commonly known as “Folinate Rescue”;
- in combination with 5-fluorouracil in cytotoxic therapy.

Note:
Persistently high serum methotrexate levels may also be expected in low-dose methotrexate therapy particularly in pleural effusions, ascites, renal insufficiency and inadequate fluid intake during methotrexate therapy.

4.2 Posology and method of administration

Posology

Disodium folinate in combination with 5-fluorouracil in cytotoxic therapy

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

Different regimens and different doses are used, without any dose having been proven to be the optimal one.

The following regimens have been used in adults and elderly in the treatment of advanced or metastatic colorectal cancer and are given as examples.

1. Weekly regimen

1.1 Moderately high-dose 5-fluorouracil

500 mg/m² folinic acid (= 546.5 mg/m² disodium folinate) as IV infusion over a period of 2 hours plus 600 mg/m² 5-fluorouracil as IV bolus injection 1 hour after the start of the disodium folinate infusion.

Repeat once a week for a total of 6 weeks (= 1 cycle).

Repeat the cycle after a 2-week treatment interval. The number of cycles will depend on the response of the tumour.

Dose adjustment of 5-fluorouracil
The 5-fluorouracil dose should be adjusted in accordance with the toxicity observed:

Gastrointestinal toxicity WHO ≥ 1:	Reduction to 500 mg/m². Resumption of therapy only when findings have completely returned to normal.
Bone marrow toxicity WHO ≥ 1:	Reduction to 500 mg/m². Resumption of therapy only when the findings are as follows: Leukocytes > 3 000/µl Thrombocytes > 100 000/µl

1.2 High-dose 5-fluorouracil

500 mg/m² folinic acid (= 546.5 mg/m² disodium folinate) as IV infusion over a period of 1-2 hours and subsequently 2 600 mg/m² 5-fluorouracil by continuous infusion over 24 hours.

Repeat once a week for a total of 6 weeks (= 1 cycle).

Repeat the cycle after a 2-week treatment interval. The number of cycles will depend on the response of the tumour.

Dose adjustment of 5-fluorouracil
The 5-fluorouracil dose should be adjusted in accordance with the toxicity observed:

Life-threatening cardiotoxicity:	Termination of therapy
Bone marrow toxicity WHO ≥ 3:	Reduction by 20% Resumption of therapy only when the findings are as follows: Leukocytes > 3 000/µl Thrombocytes > 100 000/µl
Gastrointestinal toxicity WHO ≥ 3:	Reduction by 20%

2. Monthly regimen

2.1 Moderately high-dosed disodium folinate

200 mg/m² folinic acid (= 218.6 mg/m² disodium folinate) daily, followed by 370 mg/m² 5-fluorouracil daily, both given as IV bolus injection. Repeat on 5 successive days (= 1 cycle).

Repeat the cycle after 4 weeks, 8 weeks and every 5 weeks after that. The number of cycles will depend on the response of the tumour.

Dose adjustment of 5-fluorouracil
The dose of 5-fluorouracil should be adjusted in each subsequent cycle in accordance with the toxicity (WHO) observed, as follows:

WHO toxicity 0:	Increase daily dose by 30 mg/m²
WHO toxicity 1:	Daily dose unchanged
WHO toxicity ≥ 2:	Reduce daily dose by 30 mg/m²

2.2 Low-dose disodium folinate

20 mg/m² folinic acid (= 21.86 mg/m² disodium folinate) daily, followed by 425 mg/m² 5-fluorouracil daily, both given as IV bolus injection. Repeat on 5 successive days (= 1 cycle).
Repeat the cycle after 4 weeks, 8 weeks and every 5 weeks after that. The number of cycles will depend on the response of the tumour.

Dose adjustment of 5-fluorouracil
In the absence of toxicity (especially if no significant bone marrow toxicity and no non-haematological side-effects occur in the interval) it is recommended to increase the dose of 5-fluorouracil by 10% in each case.

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

Preventing the manifestations of intoxication in methotrexate therapy (folinate rescue)

Only physicians experienced in the use of high-dose methotrexate therapy should use prophylactic disodium folinate.

The prophylactic use of disodium folinate with methotrexate may start as mentioned below, without waiting for results of methotrexate serum level monitoring, and then posology may be further adapted according to results of methotrexate serum levels when available.

The use of a dose of methotrexate at ≥ 100 mg/m² (body surface) must be followed by the administration of disodium folinate. There are no uniform recommendations for the dose and mode of use of disodium folinate as an antidote in high-dose methotrexate therapy. The following dose recommendations are therefore given as examples:

Disodium folinate rescue following the intravenous administration of methotrexate (MTX):

MTX serum levels 24 - 30 hours after administration of MTX	Disodium folinate dose (mg/m² body surface) calculated as folinic acid and dose interval (hours)	Duration of treatment
1.0 x 10^{-8} mol/l - 1.5 x 10^{-6} mol/l	10 to 15 mg/m² every 6 hours	48 hours

1.5 x 10^{-6} mol/l - 5.0 x 10^{-6} mol/l	30 mg/m² every 6 hours	up to MTX serum level < 5 x 10^{-8} mol/l
> 5.0 x 10^{-6} mol/l	60 to 100 mg/m² every 6 hours	up to MTX serum level < 5 x 10^{-8} mol/l

Start of rescue
Not later than 18 to 30 hours after the start of methotrexate intravenous administration.

End of rescue
72 hours after the start of methotrexate intravenous administration at the earliest. On completion of the rescue, the methotrexate level should be below 10^{-7} mol/l, preferably below 10^{-8} mol/l.

An "over-rescue" may impair the efficacy of methotrexate. With inadequate rescue, considerable toxic side-effects are likely with high-dosed methotrexate therapy.

Method of administration
Sodiofolin is for intravenous use only, either undiluted by injection or by infusion after dilution.

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

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

The combination of disodium folinate with 5-fluorouracil is not indicated in:
- existing contraindications against 5-fluorouracil, in particular breastfeeding,
- severe diarrhoea.

Therapy with disodium folinate 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 folinic acid with methotrexate or 5-fluorouracil during pregnancy and breastfeeding, see section 4.6 and the summaries of product characteristics for methotrexate- and 5-fluorouracil-containing medicinal products.

Disodium folinate 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.

4.4 Special warnings and precautions for use

Disodium folinate 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 folinate 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 folinate 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 folinate.

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 folinate administration and after discontinuation is recommended (see section 4.5).

Disodium folinate/methotrexate
Disodium folinate 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.

Disodium folinate 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). 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 folinate or prolonged administration may be indicated.

Excessive disodium folinate 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.

In the treatment of accidental overdose of folic acid antagonists, disodium folinate should be administered as promptly as possible. With increasing time interval between antifolate administration (e.g. methotrexate) and disodium folinate rescue the effectiveness of disodium folinate in counteracting toxicity decreases. Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with disodium folinate.

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.

Disodium folinate/5-fluorouracil
In the combination regimen with 5-fluorouracil, the toxicity profile of 5-fluorouracil may be enhanced by disodium folinate, particularly in elderly or debilitated patients. The most common manifestations are leukopenia, mucositis, stomatitis and/or diarrhoea which may be dose limiting. When disodium folinate 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. Toxicities observed in patients treated with the combination are qualitatively similar to those observed in patients treated with 5-fluorouracil 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 folinate, and supportive intravenous therapy. 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).

Combined 5-fluorouracil/disodium folinate 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.
In elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin with a reduced dose of 5-fluorouracil.

Excipient(s) with known effect

For vials with 2 ml, 4 ml:
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially "sodium-free".

For vials with 6 ml:
This medicinal product contains 29.38 mg sodium per vial, equivalent to 1.47% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For vials with 8 ml:
This medicinal product contains 39.18 mg sodium per vial, equivalent to 1.96% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For vials with 10 ml:
This medicinal product contains 48.97 mg sodium per vial, equivalent to 2.45% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For vials with 18 ml:
This medicinal product contains 88.15 mg sodium per vial, equivalent to 4.41% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

When disodium folinate 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 folinate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil.

The following side effects for disodium folinate used in conjunction with 5-fluorouracil were reported frequently: diarrhoea, dehydration, stomatitis and leukopenia. Less commonly infections, thrombocytopenia, nausea, vomiting, constipation, malaise, alopecia, dermatitis and anorexia have been observed.

Life-threatening diarrhoeas have been observed if 600 mg/m² of 5-fluorouracil (IV bolus once weekly) is given together with disodium folinate. When disodium folinate 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 folinate may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin, and succinimides, and may increase the frequency of seizures (decreased 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 breastfeeding women. No formal animal reproductive toxicity studies with disodium folinate have been conducted. There are no indications that folinic acid induces harmful effects if administered during pregnancy. During pregnancy, methotrexate or 5-fluorouracil 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 or breastfeeding, there are no limitations as to the use of disodium folinate to diminish toxicity or counteract the effects.

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

Breastfeeding
It is not known whether disodium folinate is excreted in human milk. Disodium folinate can be used during breastfeeding 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 breastfeeding. Breastfeeding must be discontinued before such treatment is initiated.

Regarding the use of disodium folinate with 5-fluorouracil, methotrexate or other folic acid antagonists during breastfeeding, please refer also to the summaries of product characteristics for these medicinal products.

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 folinate 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

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 – sensitisation, 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 folinate as solution for injection.

Combination therapy with 5-fluorouracil
Disodium folinate enhances the toxicity of 5-fluorouracil (see section 4.5). Generally, the safety profile depends on the applied regimen of 5-fluorouracil.

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

Blood and lymphatic system disorders	Very common Bone marrow failure, including fatal cases
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 folinate than the recommended dose.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment, ATC code: V 03 AF 06

Mechanism of action
Folinic acid is the formyl derivative of tetrahydrofolic acid, i.e. the active form of folic 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 folinate
Folinic acid is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as methotrexate. Folinic acid and folate antagonists share the same membrane transport carrier and compete for transport into cells, stimulating folate antagonist efflux. Folinic acid also protects cells from the effects of folate antagonist by repletion of the reduced folate pool. Folinic 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 folinate with 5-fluorouracil
5-fluorouracil inhibits *inter alia* DNA synthesis by binding thymidilate synthetase. The combination of disodium folinate with 5-fluorouracil results in the formation of a stable ternary complex consisting of thymidilate synthetase, 5-fluorodeoxy-uridinemonophosphate and 5,10-methylenetetrahydrofolate. This leads to an extended blockade of thymidilate synthetase with enhanced inhibition of DNA biosynthesis, resulting in increased cytotoxicity as compared to 5-fluorouracil monotherapy.

5.2 Pharmacokinetic properties

Absorption
A pharmacokinetic study was performed to demonstrate the bioequivalence of disodium folinate in comparison with a licensed calcium folinate reference preparation. The bioequivalence criteria determined were fulfilled in respect of the pharmacokinetic parameters for D- and L-folinic acid and for the metabolite 5-methyltetrahydrofolic acid. Calcium folinate and disodium folinate solutions are bioequivalent.

Distribution
The distribution volume of folinic acid is not known. With IV application, peak serum levels of the parent substance (D/L-formyltetrahydrofolic acid, folinic acid) are obtained after 10 minutes.

Biotransformation
The active isomeric form 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 and occurs more quickly and more completely after oral application than after parenteral application.

Elimination

The inactive isomeric form D-5-formyltetrahydrofolic acid is excreted virtually completely unchanged via the kidneys. The active isomeric form L-5-formyltetra-hydrofolic acid is in part excreted unchanged via the kidneys, but is predominantly metabolised to folic acid.

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
Hydrochloric acid
Water for injection

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 dilution (see section 6.6): 72 hours.

After mixing with 5-fluorouracil or dilution with sodium chloride 9 mg/ml (0.9%) solution for injection (see section 6.6): Chemical and physical in use stability has been demonstrated for 72 hours at 20 °C – 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.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Keep the container 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 1 of 5, 10 or 20 ml.
Closure: bromobutyl rubber stopper with aluminium flip-off cap as seal.

Vials with 2 ml, 4 ml, 6 ml, 8 ml, 10 ml or 18 ml solution for injection/infusion.
Packs containing 1 vial or 5 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Sodiofolin 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 for injection.

Sodiofolin 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(S)

<[To be completed nationally]>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

03/2024