Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sodiofolin 50 mg/ml, solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sodiofolin 50 mg/ml, solution for injection or infusion 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.
7 ml of solution contains 382.55 mg disodium folinate equivalent to 350 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.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection or 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

Sodiofolin 50 mg/ml, solution for injection or infusion is administered intravenously, either undiluted by injection or by infusion after dilution (for dilution see section 6.6). Disodium folinate should not be administered intrathecally.

Disodium folinate in combination with 5-fluorouracil in cytotoxic therapy

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

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.

1. Weekly regime

1.1 Moderately high-dose fluorouracil

500 mg/m² folinic acid (= 546.5 mg/m² disodium folinate) as i.v. infusion over a period of 2 hours plus 600 mg/m² fluorouracil as i.v. 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 fluorouracil

The fluorouracil dosage 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/microlitres Thrombocytes > 100,000/microlitres

1.2 High-dose fluorouracil

500 mg/m² folinic acid (= 546.5 mg/m² disodium folinate) as i.v. infusion over a period of 1-2 hours and subsequently 2,600 mg/m^2 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 fluorouracil

The fluorouracil dosage 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/microlitres Thrombocytes > 100,000/microlitres
Gastrointestinal toxicity WHO ≥ 3:	Reduction by 20%

2. Monthly regime

2.1 Moderately high-dosed disodium folinate

200 mg/m² folinic acid (= 218.6 mg/m² disodium folinate) daily, followed by 370 mg/m² fluorouracil daily, both given as i.v. 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 fluorouracil

The dosage of 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 fluorouracil daily, both given as i.v. 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 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 dosage of fluorouracil by 10% in each case.

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 dosage and mode of use of disodium folinate as an antidote in high-dose methotrexate therapy. The following dosage 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 dosage 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.

4.3 Contraindications

Hypersensitivity to disodium folinate or any of the excipients.

The combination of disodium folinate with fluorouracil is not indicated in:
- Existing contraindications against fluorouracil, in particular pregnancy and lactation.
- Severe diarrhoea.

Therapy with disodium folinate combined with 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).

Disodium folinate is not suitable for the treatment of pernicious anaemia or other anaemias due to Vitamin B12 deficiency. Although haematological remissions may occur, the neurological manifestations remain progressive.

4.4 Special warnings and precautions for use

Disodium folinate should only be used under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

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.

Concomitant disodium folinate will not, however, inhibit the antibacterial activity of other folic acid antagonists such as trimethoprim and pyrimethamine.

In the combination regimen with fluorouracil, the toxicity profile of fluorouracil may be enhanced or shifted by disodium folinate. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea which may be dose limiting. When disodium folinate and fluorouracil are used in combination, the fluorouracil dosage must be reduced more in cases of toxicity than when fluorouracil is used alone. Toxicities observed in patients treated with the combination are qualitatively similar to those observed in patients treated with 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 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).

Particular care should be taken in the treatment of elderly or debilitated patients, as these patients may be at increased risk of severe toxicity.

In the treatment of accidental overdosage 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.

Delayed methotrexate excretion may be caused by third space fluid accumulation (i.e., ascites, pleural effusion), renal insufficiency, inadequate hydration or non steroidal anti inflammatory or salicylates drug administration. Under such circumstances, higher doses of disodium folinate or prolonged administration may be indicated.

Disodium folinate has no effect on non-haematological toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

In epileptic patients treated with phenobarbital, phenytoine, primidone, there is a risk to increase the frequency of seizures due to decrease of plasmatic concentrations of anti epileptic drugs. Clinical monitoring, possibly monitoring of the plasmatic concentrations and if necessary, dose adaptation of the anti-epileptic drug during disodium folinate administration and after discontinuation is recommended (see 4.5)**.**

4.5 Interaction with other medicinal products and other forms of interaction

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

Concomitant use of disodium folinate counteracts the antineoplastic activity of methotrexate and increases the cytotoxic effects of fluorouracil.

The following side-effects for disodium folinate used in conjunction with fluorouracil were reported frequently: diarrhoea, dehydration, stomatitis and leucopenia. 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 fluorouracil (i.v. bolus once weekly) is given together with disodium folinate. When disodium folinate and fluorouracil are used in combination, the fluorouracil dosage must be reduced more than when fluorouracil is used alone.

Concomitant use requiring precautions for use: Phenobarbital, primidone, phenytoine: decreased plasma levels of enzymatic inductor anticonvulsivant drugs by increasing the hepatic metabolism for which folates are one of the cofactors (see 4.4).

4.6 Fertility, pregnancy and lactation

Methotrexate therapy is contra-indicated during pregnancy and lactation period. Therefore, prevention of consequences of a methotrexate therapy does not apply.
Combination therapy with disodium folinate and fluorouracil is contra-indicated during pregnancy and lactation period.

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 is unlikely to affect the ability to drive or operate machines. The general condition of the patient is likely to be more significant than any drug-induced effects.

4.8 Undesirable effects

Adverse reactions to disodium folinate are rare but occasional pyrexial reactions have been reported following parenteral administration. Isolated case of allergic reactions - sensitisation, including anaphylactoid reactions and urticaria, can occur. At high dosage gastrointestinal disorders have been observed.

Disodium folinate enhances the toxicity of 5-fluorouracil (see section 4.5 Interactions).

4.9 Overdose

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

Should overdosage of the combination of fluorouracil and Sodiofolin 50 mg/ml, solution for injection or infusion occur, overdosage instructions for fluorouracil should be followed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment
ATC code: V03 AF06

Folinic acid is the formyl derivative of tetrahydrofolic acid resp. the active form of folic acid. It is involved in various metabolic processes including purine synthesis, pyrimidine nucleotide synthesis and amino acid metabolism.

Biochemical rationale for the combination of disodium folinate with fluorouracil:

Fluorouracil inhibits *inter alia* DNA synthesis by binding thymidilate synthetase. The combination of disodium folinate with 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 fluorouracil monotherapy.

5.2 Pharmacokinetic properties

Bioequivalence
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 i.v. application, peak serum levels of the parent substance (D/L-formyltetrahydrofolic acid, folinic acid) are obtained after 10 minutes.

Metabolism
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.

Excretion
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 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 SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium hydroxide
Hydrochloric acid
Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

36 months.
After dilution (see section 6.4 and 6.6): 72 hours.

6.4 Special precautions for storage

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

After mixing with fluorouracil or dilution with 0.9 % sodium chloride 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.

6.5 Nature and contents of container

Colourless glass vials type 1 of 5, 10 and 20 ml respectively.
Closure: bromobutyl rubber stopper with aluminium flip-off cap as seal.

Vials with 2 ml, 4 ml, 6 ml, 7 ml, 8 ml, 10 ml or 18 ml solution for injection or infusion.
Packs containing 1 vial or 5 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Sodiofolin 50 mg/ml, solution for injection or infusion 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 or infusion may be diluted with 0.9 % sodium chloride solution.
Sodiofolin 50 mg/ml is compatible with fluorouracil.
Only clear solutions without visible particles should be used.

For single use only. Any unused product must be discarded.

7 MARKETING AUTHORISATION HOLDER

Medac
Gesellschaft für klinische
Spezialpräparate mbH
Fehlandtstraße 3
D-20354 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA 623/5/1

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