

**DISODIUM FOLINATE 50 MG/ML SOLUTION
FOR INJECTION OR INFUSION**

PL 11587/0024

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation (licence) for the medicinal product Disodium Folate 50 mg/ml Solution for injection or infusion (product licence number: 11587/0024).

Disodium Folate 50 mg/ml Solution for injection or infusion contains folic acid. Folic acid is used to prevent possible side effects caused by the anti-cancer medicine, methotrexate. Folic acid also increases the action of the anti-cancer medicine fluorouracil; the two substances are used in combination for special treatment of cancer.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Disodium Folate 50 mg/ml Solution for injection or infusion outweigh the risks, hence a Marketing Authorisation has been granted.

**DISODIUM FOLINATE 50 MG/ML SOLUTION FOR
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted medac a marketing authorisation for the medicinal product Disodium Folate 50 mg/ml Solution for injection or infusion (PL 11587/0024) on 21 May 2007. This medicine is available only on prescription.

Disodium folinate is indicated to diminish the toxicity and counteract the action of folic acid antagonists in cytotoxic therapy with, for example, methotrexate. Disodium folinate, in combination with 5-fluorouracil, also enhances cytotoxic activity in the palliative therapy of colorectal carcinomas.

This is a standard abridged application for Marketing Authorisation submitted under Article 10a of Directive 2001/83/EC for a solution for injection and infusion containing disodium folinate, equivalent to 50 mg/ml of folinic acid. The proposed product is identical to Sodiofolin 50 mg/ml, Solution for Injection (PL 11587/0005), which was licensed to medac on 2 August 2000.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

The active substance, folinic acid, is prepared from the acid precipitation of calcium folinate.

The active ingredient manufacturer's specifications are generally based on requirements included in the Ph Eur monograph for calcium folinate.

Satisfactory batch analyses data demonstrate compliance with the active ingredient manufacturer's specifications.

A satisfactory Certificate of Analysis has been provided for the current reference standard.

The drug substance is stored in appropriate packaging. Specifications and typical analytical test reports for the packaging are provided and are satisfactory.

Stability studies have been carried out on production-scale batches stored under long-term and accelerated conditions. The results remained within specification and the data support storage at 2-8 °C. A retest period of 2 years has been set, which is satisfactory.

DRUG PRODUCT

Description and composition of the drug product

The product is presented as a sterile solution for parenteral use, containing 54.65 mg/ml disodium folinate (equivalent to 50.0 mg/ml folinic acid). The product also contains sodium hydroxide (Ph Eur), hydrochloric acid (Ph Eur), water for injection (Ph Eur) and nitrogen (Ph Eur).

All excipients have been specified as complying with their corresponding Ph Eur monographs.

Certificates of Analysis demonstrate full compliance with current Ph Eur requirements for each excipient.

No overages are used.

None of the excipients are of animal origin. A statement confirming that the proposed disodium folinate solution for injection and infusion fully complies with current CPMP-CVMP guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products is provided.

Manufacture

The manufacturing process and in-process controls have been adequately summarised. A satisfactory flow diagram has been presented.

The proposed in-process controls and acceptance criteria are satisfactory and each batch is checked for sterility before release.

Process validation has been carried out and all results comply with the acceptance criteria, demonstrating the consistency of the manufacturing process. The process may be considered validated.

Finished product specification

The tests and controls applied in the finished product specification are appropriate for this type of product. The test methods are described and carried out in accordance with the Ph. Eur. Satisfactory validation data have been provided where appropriate. Batch analytical data demonstrate compliance with proposed specifications.

Container-closure system

The product is stored in colourless, type I glass vials of 5, 10 or 20 ml or in colourless, type I glass 6R (short), 10R or 20R vials. The vials are enclosed by bromobutyl rubber stoppers with aluminium flip-off caps. The packaging components meet Ph Eur requirements and satisfactory specifications and dimensional drawings have been provided for all primary packaging components. Acceptable certificates of conformity have been provided.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months with the storage precautions "Store at 2 - 8° C (in a refrigerator). Keep the vial in the outer carton in order to protect from light" is appropriate.

After mixing with fluorouracil or dilution with 0.9 % sodium chloride solution chemical and physical in use stability has been demonstrated for 72 hours at 20-25° C. From a microbiological point of view the product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8 °C unless dilution has taken place in controlled and validated aseptic conditions.

Bioequivalence and bioavailability

Comparative bioequivalence and bioavailability studies are not required for parenteral solutions intended solely for administration by injection using the same dosage regimen as the comparator product. However, a clinical study was carried out to investigate the pharmacokinetic characteristics and bioequivalence of disodium folinate in comparison to the pharmaceutical alternative, calcium folinate, following a single i.v. dose administered to 18 subjects.

Product literature

All product literature (Summary of Product Characteristics, labelling and Patient Information Leaflet) is satisfactory.

Assessor's conclusion

A product licence may be granted.

PRECLINICAL ASSESSMENT

No preclinical toxicity studies other than acute and local tolerance studies were performed with this product, which is considered to be acceptable given the nature of the application. The acute and local tolerance studies were performed to an acceptable standard and in accordance with Good Laboratory Practices (GLP).

CLINICAL ASSESSMENT

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.

Posology

Disodium Folate 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 of SPC). 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 the 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/ μ l
Thrombocytes > 100,000/ μ l

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/m² 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/ μ l
Thrombocytes > 100,000/ μ l
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 at 24-30 hours after administration of MTX	Disodium folinate dose (mg/m ² 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/m ² every 6 hours	48 hours
1.5 x 10 ⁻⁶ mol/l - 5.0 x 10 ⁻⁶ mol/l	30 mg/m ² 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/m ² 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 infusion intravenous administration.

End of rescue

72 hours after the start of methotrexate intravenous 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.

Clinical pharmacology

Pharmacokinetic / bioequivalence

Sodium folinate was compared with a calcium folinate-based product (Rescuvinol, Lösung). Eighteen normal volunteers were divided into two groups of nine; each group had a different order of infusions. Each subject received a dose equivalent to $200\text{mg}/\text{m}^2$ folinic acid over 15 minutes. AUC_{0-t} , C_{max} and terminal elimination half-life were measured. Three plasma constituents were estimated: d – CHO – THF, 1 – CHO – THF and CH_3 – THF (methylene tetrahydrofolate; the main metabolite).

The geometric mean ratios were:

	d – CHO – THF	1 – CHO THF	CH₃ THF
AUC	94% (89-99)	98% (93-103)	96% (89-104)
C_{max}	92% (88-98)	96% (89-104)	99% (93-106)

(The 90% confidence intervals are in brackets)

It can be seen that all the criteria for bioequivalence are fulfilled for all three of the folinic acid metabolites. The terminal elimination half-life was also indistinguishable for each of the three metabolites. Intravenous sodium folinate was, therefore, shown to be bioequivalent to a formulation of calcium folinate that is licenced in Germany (Rescuvinol).

Efficacy

The applicant submitted a single open, non-randomized trial of disodium folinate in patients with advanced colorectal carcinoma.

Aim

To determine efficacy, toxicity and practicability of a simultaneous 24 hour infusion of 5-fluorouracil (5-FU) and disodium folinate (DSF) in patients with advanced colorectal carcinoma.

Design and methods

Open, non-controlled, non-randomized, single-treatment, multi-centre, phase II study in 51 patients over 18 years with unresectable, metastasised colorectal cancer or inoperable local recurrence. Patients with either histologically established metastases or typical metastatic findings on objective imaging techniques, without previous chemotherapy (exception of

adjuvant chemotherapy/radiation therapy completed more than 6 months previously) were enrolled at five centres. Chemotherapy was started no later than 4 weeks after initial investigations and patients received 5FU (2600mg/m²) and DSF (500mg/m² folinic acid) mixed in a single infusion pump and applied once weekly either as in patients or out patients for 24 hours over 6 weeks followed by a 2-week rest period. Each 8-week period represented one cycle of therapy. Cycles were repeated until progression of disease was established. For patients with complete remission, an additional cycle was given and, if new tumour progression was seen in this sub-group of patients, treatment was to be continued. Following cessation of treatment, all patients were followed up every 3 months until death.

The drugs were infused via a subcutaneous port chamber. Appropriate laboratory monitoring to assess haematotoxicity occurred and side effects were examined at each patient visit.

WHO remission criteria were used, with the primary efficacy variable being objective tumour response rate – the sum of complete and partial remissions. The study size was based on Simon’s optimal 2-stage designs for phase II clinical trials (R Simon 1989). Based on previous studies in this patient population, the baseline response of 20% was selected and a desirable efficacy target of 40%, with α (probability of failing to reject a treatment with response probability <20%) and 5% with β (probability of rejecting the treatment with response rate >40%). The optimal design had a maximum sample size of 38 patients with first recruitment stage of 18 patients with trial termination if the number of responses was <3. The null hypothesis would be rejected if the number of responses within the 38 patients exceeded 9 (a therapy with a true response probability of 20% would give a probability of early study termination of 50.1%).

Results

At the time of study reporting, follow-up was ongoing. Forty-five of 51 patients had disease progression. Six patients were censored after their last follow-up examination without progression. All 51 patients started therapy. There were three serious protocol violations because of missing tumour re-staging. Twenty-nine of 51 patients (57%) had colon cancer, 20/51 (39%) had rectal tumours and one patient (2%) had combined primary tumours. Ten patients had previously received systemic adjuvant therapy with 5FU/FA and two patients had other prior adjuvant therapy, that is, 39/51 (76%) had no prior chemotherapy. Treatment cycles varied between 1 and 9, with a median of 3 and mean of 3.5 cycles. One hundred and seventy-nine cycles were given. After start of therapy, median follow-up time was 20.2 months, with a range for survivors of 11-24.3 months.

ITT Efficacy Analysis

Within the first patient cohort, 7/18 patients showed partial responses and trial recruitment was continued as planned to 38 patients. In this patient set, 15/38 showed responses (two complete responses, 13 partial responses). Because of these favourable results, a decision to study up to 51 patients was made to estimate the proportion, extent and durability of response to 51 patients.

Best Response	N	%	95% CI
CR	2	4	0.3-16
PR	17	33	19-51
NC	21	41	
PD	8	16	6-31
Not evaluable	3	6	

<i>Total</i>	51	100	
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CR, complete response; PR, partial response; NC, no change; PD, progressive disease

The objective best response (CR+PR) showed a response rate of 37% (95% CI 24-52). Responses to therapy lasted for a median of 7.2 months (95% CI 4.3-10.0). Kaplan-Meier analysis showed time to progression of 7.3 months median (95% CI 6.3-8.3) and median time to death was 16.5 months (95% CI 10.2-22.8).

Assessor's comment

The objective remission rate of 37% compares well with the study results obtained by Ardalan (1991) using 5-FU and calcium folinate (leucovorin). Further trials using folinic acid infusion given prior to 24h 5-FU infusion are as follows:

Author	No of patients	Response rate	
			CR + PR + NC [n (%)]
Ardalan, 1991	12	7 (58%)	Not given
Weh, 1994	21	8 (38%)	16 (76%)
Stoffregen, 1996*	44	16 (36%)	36 (82%)
Weh 1998**	64	15 (23%)	52 (81%)
Kohne, 1998 (2)	91	40 (44%)	71 (78%)
MC-NF.1/CC	51	19 (37%)	40 (78%)

*200 mg/m² FA + 2000 mg/m² 5-FU

**1 cycle consisted of 4 weekly infusions of 5-FU/FA + 2 weeks rest

CR, complete response; PR, partial response; NC, no change

Other parameters of median response, median time to progression and median overall survival were comparable to those reported in the studies above where calcium folinate was used instead of DSF in the first-line treatment in patients with colorectal carcinoma. The study showed that 24-hour continuous infusion with high-dose 5-FU and DSF was effective in the first-line therapy of patients with advanced and/or metastatic colorectal cancer.

Safety

No unexpected therapy-related adverse events or treatment-related deaths were observed. The quality and quantity of the most frequently reported therapy-related side effects were similar in this trial to those reported in six other trials using Ardalan-like treatment schedules. The simultaneous use of 5-FU and DSF mixed together does not result in crystallization or infusion catheter obstruction.

Expert report

The Clinical Expert Report is an excellent review of the clinical trial data.

Product literature

All product literature (Summary of Product Characteristics, labelling and Patient Information Leaflet) is satisfactory.

Discussion

The clinical data supplied, together with the accompanying clinical expert report, are sufficient to conclude that, in comparison to historical published data using the Ardalán method of administration of 5-FU and calcium folinate, equivalent efficacy has been shown.

Safety data show similar and comparable adverse event profiles but additionally a definite clinical benefit has been shown in administration of the drug in that 5-FU and sodium folinate can be admixed in one infusion bag without the precipitation seen using calcium folinate where separate infusion lines are required. The risk/benefit ratio is thus improved.

The clinical expert has made a fair appraisal of the data derived from the clinical studies and the published papers. His overall conclusions, including the benefit/risk assessment, appear to be well judged.

The data presented here are sufficient to establish the efficacy and safety of Disodium Folate 50 mg/ml Solution for injection or infusion indicated for enhancement of fluorouracil cytotoxicity and for preventing the manifestations of intoxication in methotrexate therapy.

Conclusions

A Marketing Authorisation may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Disodium Folate 50 mg/ml Solution for injection or infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No preclinical toxicity studies other than acute and local tolerance studies were performed with this product, which is considered to be acceptable given the nature of the application. The acute and local tolerance studies were performed to an acceptable standard and in accordance with Good Laboratory Practices (GLP).

EFFICACY AND SAFETY

The efficacy of disodium folinate has been well documented in the past. No new or unexpected safety concerns arise from this application.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been demonstrated for Disodium Folate 50 mg/ml Solution for injection or infusion in the therapeutic indications proposed. The risk benefit is therefore considered to be positive.

**DISODIUM FOLINATE 50 MG/ML SOLUTION FOR
INJECTION OR INFUSION**

PL 11587/0024

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 2 June 2003
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 16 July 2003
3	Following assessment of the application the MHRA requested further information on the dossier on 10 September 2003. The applicant responded to the MHRA's requests, providing further information on 5 April 2004.
4	The MHRA requested further information on the dossier on 3 December 2004. The applicant responded to the MHRA's requests, providing further information on 19 January 2005.
5	The MHRA requested further information on the dossier on 3 February 2006. The applicant responded to the MHRA's requests, providing further information on 10 May 2006.
6	The MHRA requested further information on the dossier on 9 February 2007. The applicant responded to the MHRA's requests, providing further information on 3 May 2007.
7	The MHRA requested further information on the dossier on 8 May 2007. The applicant responded to the MHRA's requests, providing further information on 8 May 2007.
8	The application was determined on 21 May 2007.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Disodium Folate 50 mg/ml Solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Disodium Folate 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 "Folate 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

Disodium Folate medac 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 the 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 \geq 1:	Reduction to 500 mg/m ² . Resumption of therapy only when findings have completely returned to normal.
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Bone marrow toxicity WHO \geq 1:	Reduction to 500 mg/m ² . Resumption of therapy only when the findings are as follows: Leukocytes > 3,000/ μ l Thrombocytes > 100,000/ μ l
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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/m² 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/ μ l
	Thrombocytes > 100,000/ μ l
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/m ²
WHO toxicity 1:	Daily dose unchanged
WHO toxicity ≥ 2 :	Reduce daily dose by 30 mg/m ²

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 $\geq 100 \text{ mg/m}^2$ (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 at 24-30 hours after administration of MTX	Disodium folinate dose (mg/m^2 body surface) calculated as folinic acid and dosage interval (hours)	Duration of treatment
$1.0 \times 10^{-8} \text{ mol/l}$ - $1.5 \times 10^{-6} \text{ mol/l}$	10 to 15 mg/m^2 every 6 hours	48 hours
$1.5 \times 10^{-6} \text{ mol/l}$ - $5.0 \times 10^{-6} \text{ mol/l}$	30 mg/m^2 every 6 hours	up to MTX serum level $< 5 \times 10^{-8} \text{ mol/l}$
$> 5.0 \times 10^{-6} \text{ mol/l}$	60 to 100 mg/m^2 every 6 hours	up to MTX serum level $< 5 \times 10^{-8} \text{ mol/l}$

Start of rescue

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

End of rescue

72 hours after the start of methotrexate intravenous 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* for palliative treatment of colorectal carcinoma 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 the treatment of colorectal cancer, 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 colorectal cancer 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, phenytoin, primidon, there is a risk to increase the frequency of seizures due to decrease of plasma concentrations of anti-epileptic drugs. Clinical monitoring, possibly monitoring of the plasma 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. Interactions 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 the treatment of colorectal cancer, the *fluorouracil* dosage must be reduced more than when *fluorouracil* is used alone.

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

4.6. Pregnancy and lactation

Methotrexate therapy is contra-indicated during pregnancy and lactation. Therefore, prevention of consequences of methotrexate therapy does not apply.

Combination therapy with disodium folinate and *fluorouracil* is contra-indicated during pregnancy and lactation.

No information is available on the effects of folic 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 cases of allergic reactions - sensitisation, including anaphylactoid reactions and urticaria- can occur. At high dosage, gastrointestinal disorders have been observed.

Disodiumfolinate 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 Disodium Folate medac 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: Antidote
ATC code: V 03 AF

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 and may be exchanged within the scope of any intended therapy.

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-formyltetrahydrofolic 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

Disodium Folate 50 mg/ml, solution for injection or infusion should not be mixed with any other drug, unless compatibility has been satisfactorily demonstrated.

Accordingly, it 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 vial 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

Disodium Folate 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.

Disodium Folate 50mg/ml, solution for injection or infusion 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

PL/11587/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/05/2007

10 DATE OF REVISION OF THE TEXT

21/05/2007

PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Disodium Folinatate 50 mg/ml, solution for injection or infusion
(Folic acid)

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Disodium Folinatate 50 mg/ml is and what it is used for
2. Before you use Disodium Folinatate 50 mg/ml
3. How to use Disodium Folinatate 50 mg/ml
4. Possible side effects
5. How to store Disodium Folinatate 50 mg/ml
6. Further Information

1. WHAT DISODIUM FOLINATE 50 MG/ML IS AND WHAT IT IS USED FOR

Folic acid, a derivative of the vitamin B12 group, is an antidote to the anticancer medicine methotrexate (rescue therapy).

Folic acid increases the action of the anticancer medicine fluorouracil; the two substances are used in combination for special treatment of cancer.

Disodium Folinatate 50 mg/ml, solution for injection or infusion has been prescribed by your doctor:
- Either for the prevention of possible side-effects resulting from methotrexate therapy
- or for special treatment of cancer in combination therapy with fluorouracil.

2. BEFORE YOU USE DISODIUM FOLINATE 50 MG/ML

Disodium Folinatate 50 mg/ml, solution for injection or infusion will not be used:
if you are allergic (hypersensitive) to disodium foinatate or any of the other ingredients of Disodium foinatate 50 mg/ml.

Disodium Folinatate 50 mg/ml, solution for injection or infusion will not be prescribed in combination with fluorouracil
- if contra-indications against fluorouracil exist, in particular if the women that you do not tolerate fluorouracil or if you are suffering from diarrhoea, nausea, vomiting or stomatitis (mouth ulcers). Your doctor will monitor these symptoms until they resolve.

Disodium Folinatate 50 mg/ml, solution for injection or infusion is not suitable for the treatment of certain blood disorders (pernicious anaemia or other anaemias due to shortage of vitamin B₁₂).

Take special care with Disodium Folinatate 50 mg/ml

Disodium Folinatate 50 mg/ml, solution for injection or infusion is used for the treatment of cancer in combination with fluorouracil. You must be aware that, as with other anticancer medicines, this combination will cause side-effects (see point 4 of this leaflet). Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

The effectiveness of some medicines (phenytoin, primidone and phenobarbital) used to treat convulsion (epilepsy) may also be reduced.

Using other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

Disodium Folinatate 50 mg/ml, solution for injection or infusion has no negative effect on pregnant or breast-feeding women. Disodium Folinatate 50 mg/ml, solution for injection or infusion in combination with fluorouracil is not recommended if you are pregnant, planning to become pregnant or while you are breast-feeding.

Driving and using machines

Your ability to drive or operate machinery is not affected by

Disodium Folinatate 50 mg/ml, solution for injection or infusion. But you should consider your general condition before driving or operating machinery.

3. HOW TO USE DISODIUM FOLINATE 50 MG/ML

Disodium Folinatate 50 mg/ml, solution for injection or infusion will be given to you
- by an injection into your vein (intravenous injection) or
- by a drip given into a vein (intravenous infusion).

The dose given depends on your size. It varies with your surface area. Technically, this is measured in square metres (m²), but actually is worked out from your height and weight.

Preventing possible side-effects during a therapy with methotrexate (rescue treatment)

Your doctor uses Disodium Folinatate 50 mg/ml, solution for injection or infusion as a preventive treatment, which follows the administration of methotrexate. Disodium Folinatate 50 mg/ml, solution for injection or infusion is given intravenously. The used amount depends on the measured methotrexate blood levels.

Start of rescue treatment: Not later than 18 to 30 hours after the start of methotrexate infusion.
End of rescue treatment: 72 hours after the start of methotrexate infusion at the earliest.

Treatment of cancer in combination with fluorouracil
All dosage schedules regarding the treatment of cancer have been determined by clinical studies carried out in large numbers of patients. Your doctor can choose from weekly,

<p>monthly or other regimens. All schedules use a combination of the two substances disodium folinate (Disodium Folate 50 mg/ml, solution for injection or infusion) and fluorouracil.</p> <p>The most frequently used schedules are:</p> <ol style="list-style-type: none"> 1. Weekly schedule of fluorouracil and Disodium Folate 50 mg/ml, solution for injection or infusion. This involves either: <ul style="list-style-type: none"> - a 2 hour intravenous infusion (‘ drip’) of Disodium Folate 50 mg/ml, solution for injection or infusion, followed by a single intravenous injection of fluorouracil (Moderately high dose fluorouracil treatment); - a 2 hour intravenous infusion of Disodium Folate 50 mg/ml, solution for injection or infusion, followed by a 24 hour infusion of fluorouracil (High dose fluorouracil treatment). 2. Monthly schedule of fluorouracil and Disodium Folate 50 mg/ml, solution for injection or infusion. <ul style="list-style-type: none"> - This involves single intravenous injections of Disodium Folate 50 mg/ml, solution for injection or infusion, followed by a single intravenous injection of fluorouracil given once a day together for 5 successive days (= 1 cycle). The cycle is repeated after 4 weeks, and then according to the response of the tumour. 	<p>This schedule may be followed at a higher dosage (Moderately high dose Disodium Folate 50 mg/ml, solution for injection or infusion) or alternatively, at a lower dosage (Low dose Disodium Folate 50 mg/ml, solution for injection or infusion).</p> <p>If more Disodium Folate 50 mg/ml was used than prescribed in this leaflet.</p> <p>When using methotrexate an overdose of disodium folinate may result in a decrease of efficacy of methotrexate (‘over-rescue’).</p> <p>No special measures are required in the event of overdose of Disodium Folate 50 mg/ml, solution for injection or infusion alone.</p>	<p>Occasional raised temperature has been seen after injection and allergic reactions can occur (e.g. itchy skin rash, swelling of the face, hands, lips with or without wheezing or light-headedness).</p> <p>Disodium Folate 50 mg/ml, solution for injection or infusion can enhance the side-effects of the anti-cancer effects of fluorouracil. The most frequent side-effects are: nausea, vomiting, diarrhoea, stomatitis (oral ulceration) and leucopenia (decrease in the number of white blood cells). Less commonly infections, thrombocytopenia (decrease in the number of platelets), anaemia (with or without vomiting, constipation, feeling generally unwell), alopecia (loss of hair), dermatitis (inflammation of the skin) and anorexia (lack of appetite) have been observed.</p> <p>If you experience stomatitis (mild to moderate oral ulceration) or diarrhoea (watery stools or bowel movements) two times per day, be sure to consult your doctor immediately.</p>	<p>Do not use Disodium folinate 50 mg/ml 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.</p> <p>Do not use Disodium folinate if you notice that it is not a clear to slightly yellow solution, free from visible particles.</p> <p>Medicines should not be disposed via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.</p>
<p>4. POSSIBLE SIDE EFFECTS</p> <p>Like all medicines, Disodium Folate 50 mg/ml can cause side effects, although not everybody gets them.</p> <p>If any of the side effects get serious please tell your doctor or pharmacist.</p> <p>If side effects last and trouble you, please inform your doctor or pharmacist. Some side effects may need treatment.</p> <p>Some side effects that have been reported following treatment with Disodium Folate 50 mg/ml are listed below:</p>	<p>6. FURTHER INFORMATION</p> <p>What Disodium folinate 50 mg/ml contains</p> <p>The active substance is disodium folinate. The other ingredients are: sodium hydroxide, hydrochloric acid and water for injections.</p>	<p>5. HOW TO STORE DISODIUM FOLINATE 50 MG/ML</p> <p>Keep out of the reach and sight of children.</p> <p>Store in a refrigerator (2°C - 8°C).</p> <p>Keep the vial in the outer carton in order to protect from light.</p>	<p>What Disodium folinate 50 mg/ml looks like and content of the pack</p> <p>Disodium Folate 50 mg/ml is a clear, colourless to slightly yellow solution for injection or infusion. It is marketed in glass vials (type I).</p> <p>Disodium Folate 50 mg/ml, solution for injection or infusion contains 54.66 mg/ml disodium folinate, equivalent to 50 mg/ml of folic acid.</p> <p>2 ml of solution contains 100.3 mg disodium folinate equivalent to 100 mg folic acid.</p> <p>4 ml of solution contains 216.6 mg disodium folinate equivalent to 200 mg folic acid.</p>

6 ml of solution contains 327.9 mg disodium folinate equivalent to 300 mg folic acid.
7 ml of solution contains 362.55 mg disodium folinate equivalent to 350 mg folic acid.
8 ml of solution contains 437.2 mg disodium folinate equivalent to 400 mg folic acid.
10 ml of solution contains 546.5 mg disodium folinate equivalent to 500 mg folic acid.
18 ml of solution contains 983.7 mg disodium folinate equivalent to 900 mg folic acid.

Pack sizes:
Vials with 2 ml, 4 ml, 6 ml, 7 ml, 8 ml, 10 ml and 18 ml solution for injection or infusion in packs of 1 or 5 vials. Not all pack sizes may be marketed.

Product Licence Number:
PL 11587/0024

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder	Manufacturer
m e d a c Gesellschaft für klinische Spezialpräparate mbH Fehlandstraße 3 D-20354 Hamburg Germany	medac Gesellschaft für klinische Spezialpräparate mbH Theaterstraße 6 D-22880 Wedel Germany

This leaflet was last approved in May 2007.

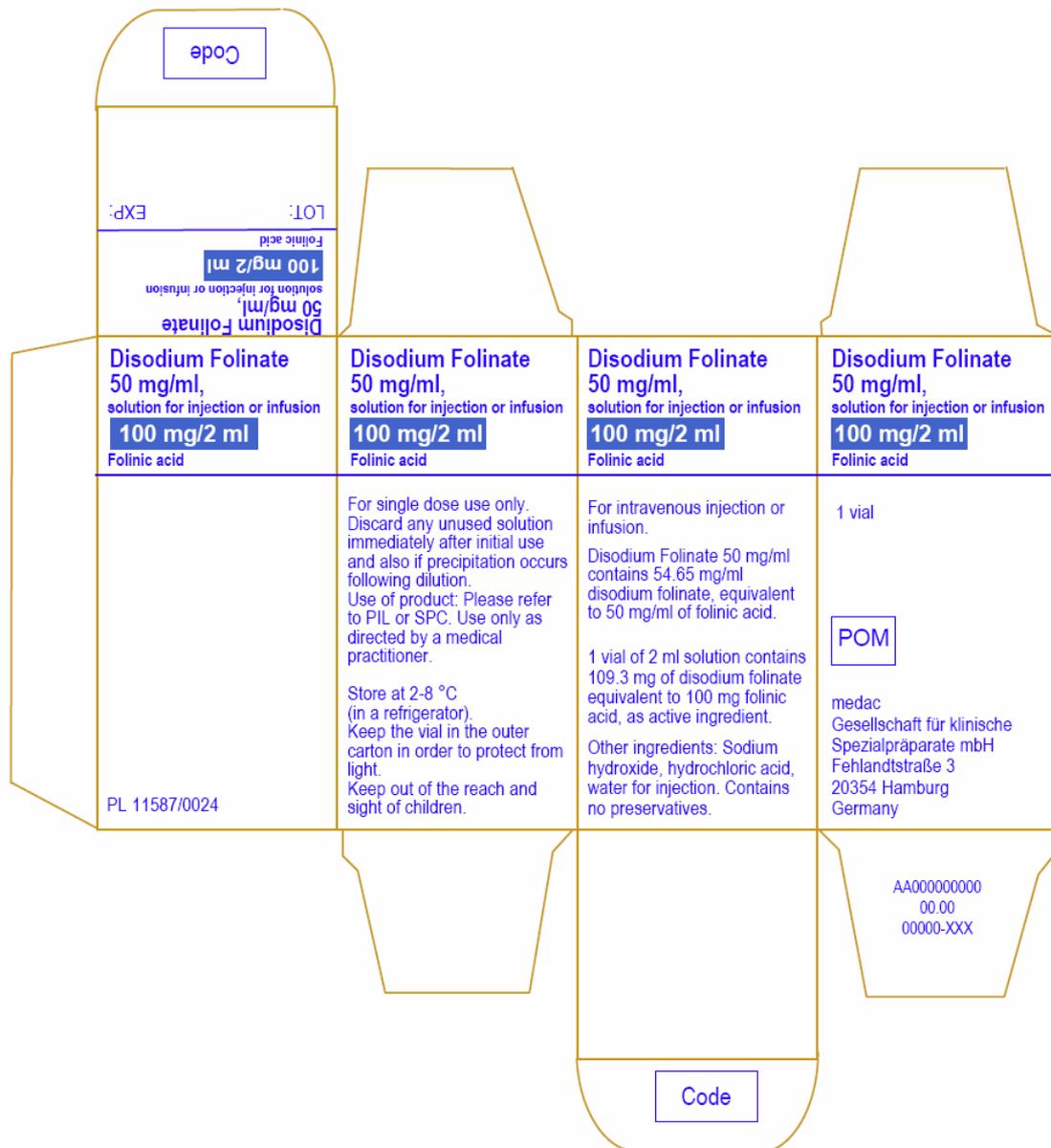
LABELLING

100mg

Vial

LOT:	Disodium Folate 50 mg/ml, solution for injection or infusion Folinic acid	AA00000000 00.00 00000-XXX
EXP:	100 mg/2ml 1 vial of 2 ml solution contains 109.3 mg of disodium folinate equivalent to 100 mg folinic acid. For intravenous injection or infusion after dilution. For single dose only. medac GmbH, Fehlandtstraße 3, 20354 Hamburg, Germany	

Carton:

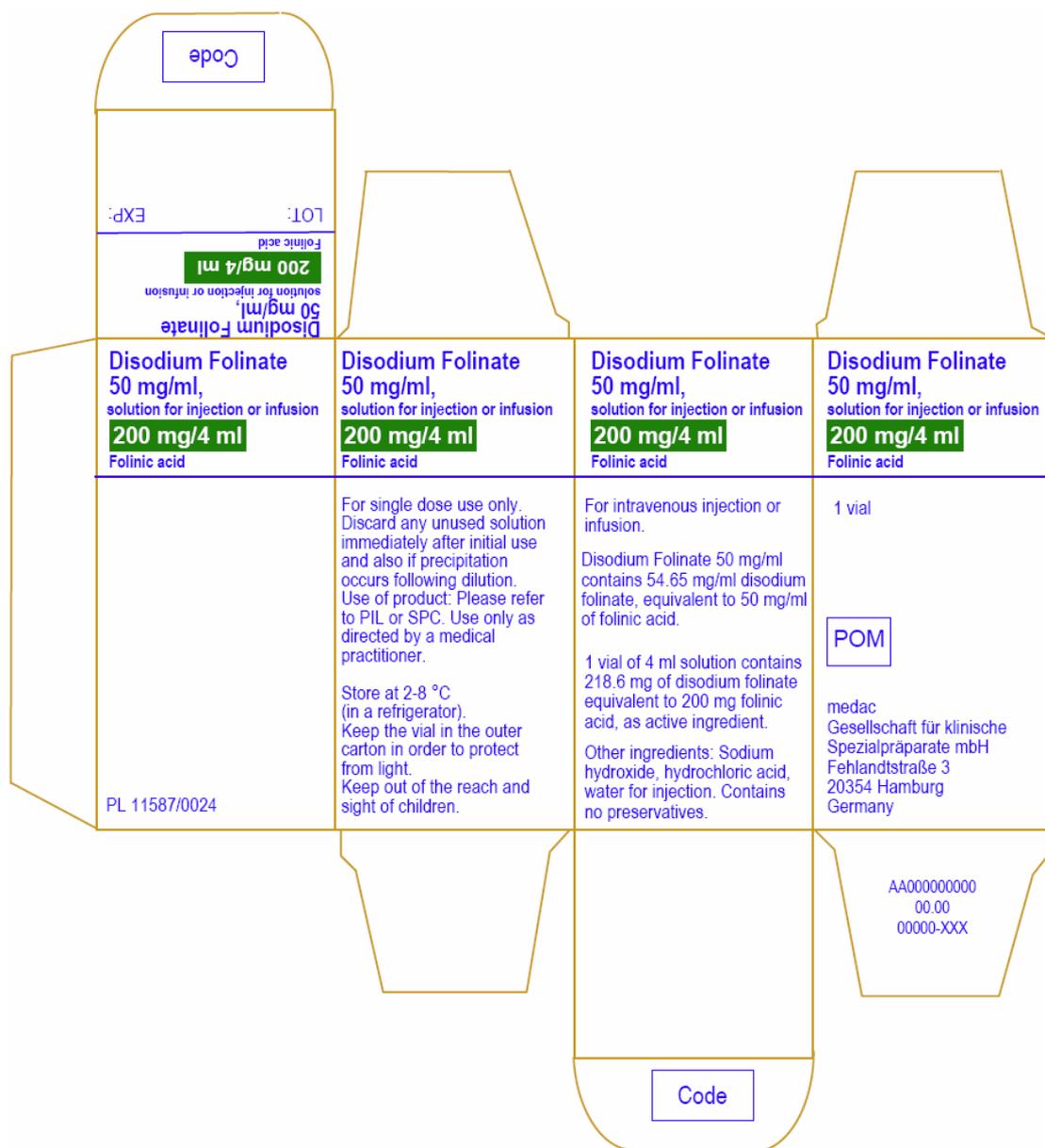


200mg

Vial

LOT:	Disodium Folate 50 mg/ml, solution for injection or infusion Folinic acid	AA00000000 00.00 0000-XXX
EXP:	200 mg/4 ml 1 vial of 4 ml solution contains 218.6 mg of disodium folinate equivalent to 200 mg folinic acid. For intravenous injection or infusion after dilution. For single dose only. medac GmbH, Fehlandtstraße 3, 20354 Hamburg, Germany	

Carton:

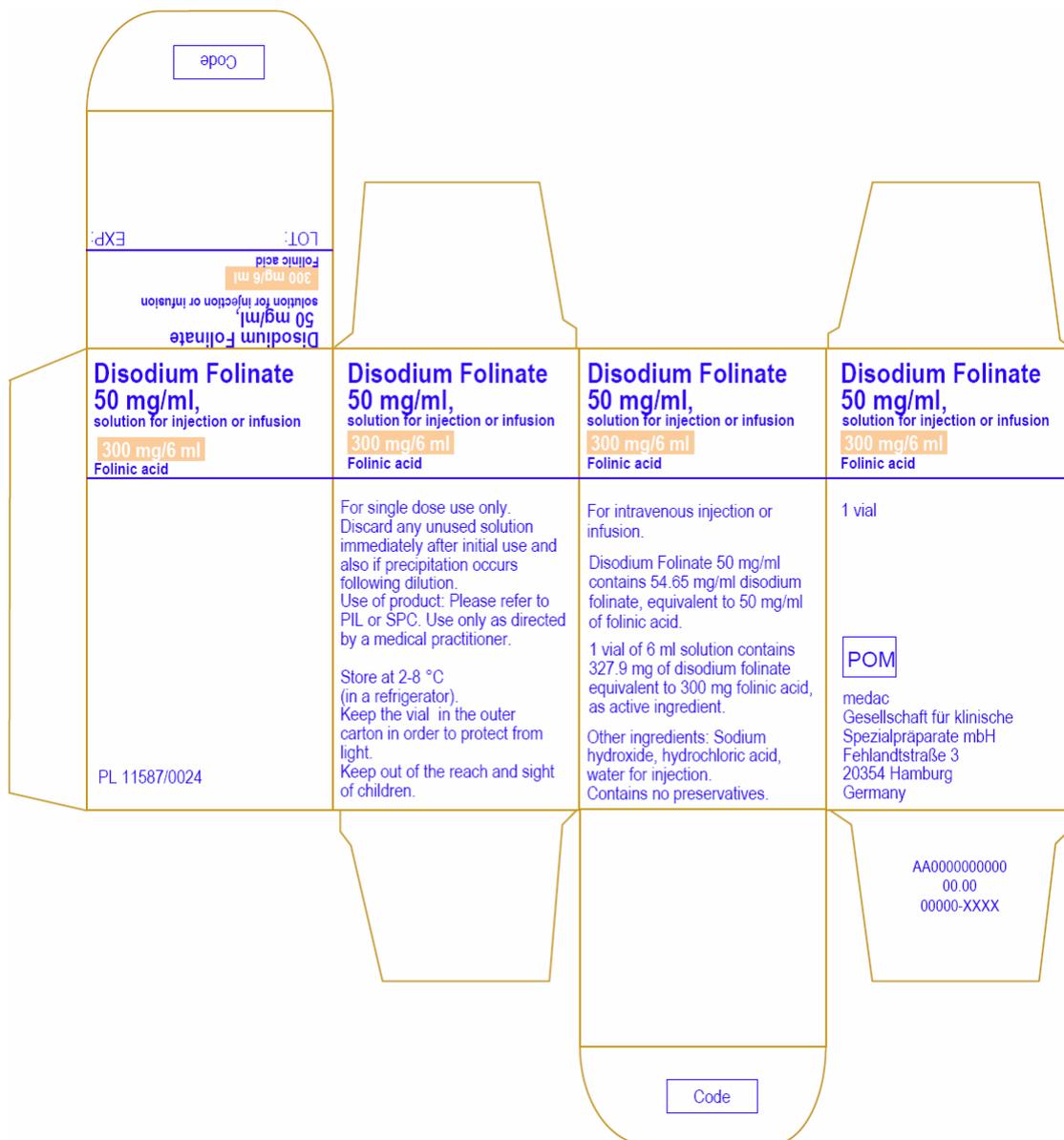


300mg

Vial:

LOT:	Disodium Folate 50 mg/ml, solution for injection or infusion Folinic acid	AA000000000 00.00 00000-XXX
	300 mg/6 ml	
	1 vial of 6 ml solution contains 327.9 mg of disodium folinate equivalent to 300 mg folinic acid.	
	For intravenous injection or infusion after dilution. For single dose only.	
EXP:	medac GmbH, Fehlandtstraße 3, 20354 Hamburg, Germany	<div style="border: 1px solid black; padding: 5px; display: inline-block;">Code</div>

Carton:

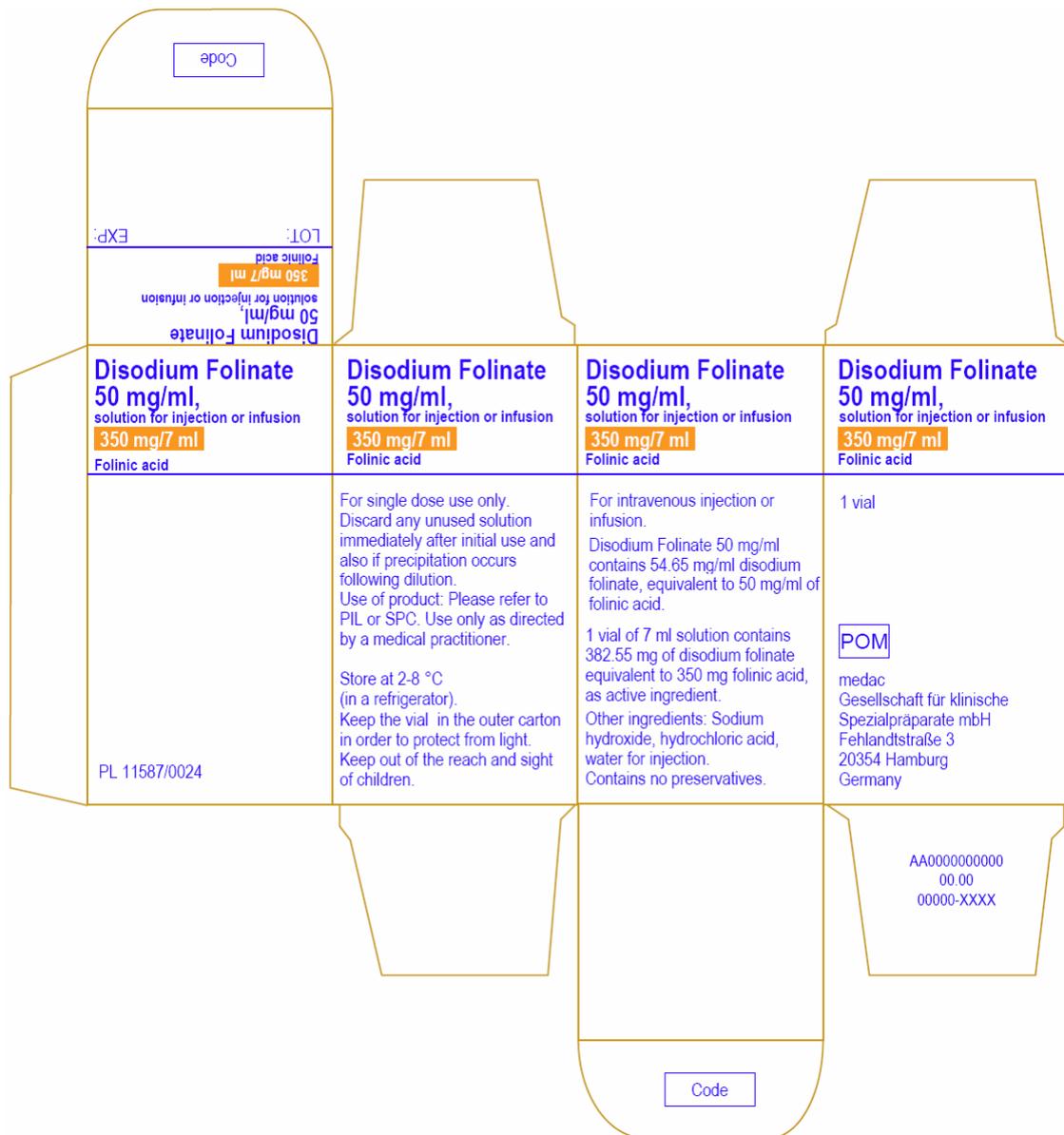


350 mg

Vial

LOT:	Disodium Folate 50 mg/ml, solution for injection or infusion Folinic acid	AA000000000 00.00 00000-XXX
<hr style="border: 1px solid blue;"/>		
<p>1 vial of 7 ml solution contains 382.55 mg of disodium folinate equivalent to 350 mg folinic acid.</p> <p>For intravenous injection or infusion after dilution. For single dose only.</p>		
EXP:	medac GmbH, Fehlandtstraße 3, 20354 Hamburg, Germany	<div style="border: 1px solid blue; padding: 5px; display: inline-block;">Code</div>

Carton:



400 mg

Vial:

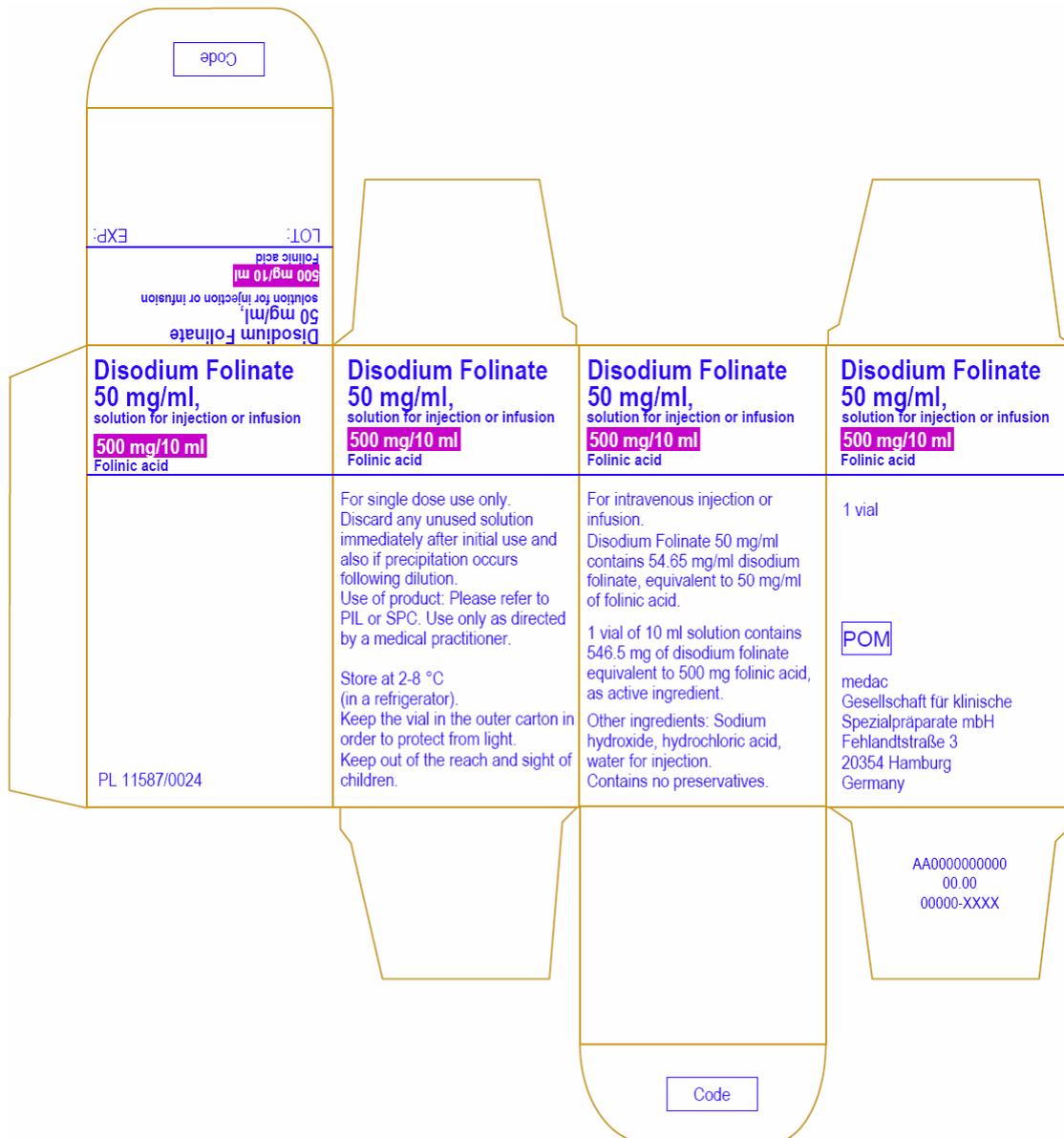
LOT:	Disodium Folate 50 mg/ml, solution for injection or infusion Folinic acid	AA000000000 00.00 00000-XXX
	400 mg/8 ml	
	1 vial of 8 ml solution contains 437.2 mg of disodium folinate equivalent to 400 mg folinic acid.	
	For intravenous injection or infusion after dilution. For single dose only.	
EXP:	medac GmbH, Fehlandtstraße 3, 20354 Hamburg, Germany	<div style="border: 1px solid black; padding: 5px; display: inline-block;">Code</div>

500mg

Vial:

LOT:	Disodium Folate 50 mg/ml, solution for injection or infusion Folinic acid	AA000000000 00.00 00000-XXX
500 mg/10 ml		
1 vial of 10 ml solution contains 546.5 mg of disodium folinate equivalent to 500 mg folinic acid.		
For intravenous injection or infusion after dilution. For single dose only.		
EXP:	medac GmbH, Fehlandtstraße 3, 20354 Hamburg, Germany	Code

Carton:



900 mg

Vial:

LOT:	Disodium Folate 50 mg/ml, solution for injection or infusion Folinic acid	AA00000000 00.00 00000-XXX
	900 mg/18 ml	
	1 vial of 18 ml solution contains 983.7 mg of disodium folinate equivalent to 900 mg folinic acid.	
	For intravenous injection or infusion after dilution. For single dose only.	
EXP:	medac GmbH, Fehlandtstraße 3, 20354 Hamburg, Germany	<input type="text" value="Code"/>

Carton:

