Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

VoriNa 25 mg/ml, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution for injection contains disodium folinate equivalent to 25.00 mg folinic acid.
One vial of 2 ml contains disodium folinate equivalent to 50 mg folinic acid
One vial of 4 ml contains disodium folinate equivalent to 100 mg folinic acid
One vial of 14 ml contains disodium folinate equivalent to 350 mg folinic acid
One vial of 20 ml contains disodium folinate equivalent to 500 mg folinic acid
One vial of 40 ml contains disodium folinate equivalent to 1000 mg folinic acid

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear yellow solution, free of particles.

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, this procedure is commonly known as "Folinate Rescue"

- in combination with 5-fluorouracil in cytotoxic therapy.

4.2 Posology and method of administration

Posology

Folinic acid rescue in methotrexate therapy:
Since the folinate rescue dosage regimen depends heavily on the posology and method of the intermediate- or high-dose methotrexate administration, the methotrexate protocol will dictate the dosage regimen of folinate rescue. Therefore, it is best to refer to the applied intermediate or high dose methotrexate protocol for posology and method of administration of folinate.
As far as these protocols mention calcium folinate dosages, calcium-folinate can be replaced by disodium folinate (VoriNa) using the same folinate dosages.
The following guidelines may serve as an illustration of regimens used in adults, elderly and children:

Folinate rescue has to be performed by parenteral administration in patients with malabsorption syndromes or other gastrointestinal disorders where enteral absorption is not assured. Dosages above 25-50 mg should be given parenterally due to saturable enteral absorption of disodium folinate.

Folinate rescue is necessary when methotrexate is given at doses exceeding 500 mg/m^2 body surface and should be considered with doses of 100 mg — 500 mg/m^2 body surface.

Dosage and duration of folinate rescue primarily depend on the type and dosage of methotrexate therapy, the occurrence of toxicity symptoms, and the individual excretion capacity for methotrexate. As a rule, the first dose of

disodium folinate is 15 mg (6-12 mg/m^2) to be given 12-24 hours (24 hours at the latest) after the beginning of methotrexate infusion. The same dose is given every 6 hours throughout a period of 72 hours. After several parenteral doses treatment can be switched over to the oral form.

In addition to disodium folinate administration, measures to ensure the prompt excretion of methotrexate (maintenance of high urine output and alkalinisation of urine) are integral parts of the folinate rescue treatment. Renal function should be monitored through daily measurements of serum creatinine.

Forty-eight hours after the start of the methotrexate infusion, the residual methotrexate-level should be measured. If the residual methotrexate-level is >0.5 µmol/l, disodium folinate dosages should be adapted according to the following table:

Residual methotrexate blood level 48 hours after the start of the methotrexate administration:	Additional disodium folinate to be administered every 6 hours for 48 hours or until levels of methotrexate are lower than 0.05 µmol/l:
≥ 0.5 µmol/l	15 mg/m^2
≥ 1.0 µmol/l	100 mg/m^2
≥ 2.0 µmol/l	200 mg/m^2

In combination with 5-fluorouracil in cytotoxic therapy:
Different regimens and different dosages are used, without any dosage 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. There are no data on the use of these combinations in children:

Bimonthly regimen: folinate 200 mg/m^2 by intravenous infusion over two hours, followed by bolus 400 mg/m^2 of 5-FU and 22-hour infusion of 5-FU (600 mg/m^2) for 2 consecutive days, every 2 weeks on days 1 and 2.

Weekly regimen: folinate 20 mg/m^2 by bolus i.v. injection or 200 to 500 mg/m^2 as i.v. infusion over a period of 2 hours plus 500 mg/m^2 5-fluorouracil as i.v. bolus injection in the middle or at the end of the folinate infusion.

Monthly regimen*:* folinate 20 mg/m^2 by bolus i.v. injection or 200 to 500 mg/m^2 as i.v. infusion over a period of 2 hours immediately followed by 425 or 370 mg/m^2 5-fluorouracil as i.v. bolus injection during five consecutive days.

For the combination therapy with 5-fluorouracil, modification of the 5-fluorouracil dosage and the treatment-free interval may be necessary depending on patient condition, clinical response and dose limiting toxicity as stated in the product information of 5-fluorouracil. A reduction of disodium folinate dosage is not required.

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

Antidote to the folic acid antagonists trimetrexate, trimethoprime, and pyrimethamine:
Trimetrexate toxicity:
- Prevention: disodium folinate should be administered every day during treatment with trimetrexate and for 72 hours after the last dose of trimetrexate. Disodium folinate can be administered either by the intravenous route at a dose of 20 mg/m^2 for 5 to 10 minutes every 6 hours for a total daily dose of 80 mg/m^2, or by oral route with four doses of 20 mg/m^2 administered at equal time intervals. Daily doses of disodium folinate should be adjusted depending on the haematological toxicity of trimetrexate.
- Overdosage (possibly occurring with trimetrexate doses above 90 mg/m2 without concomitant administration of disodium folinate): after stopping trimetrexate, disodium folinate 40 mg/m2 IV every 6 hours for 3 days.

Trimethoprime toxicity:
- After stopping trimethoprime, 3-10 mg/day disodium folinate until recovery of a normal blood count.

Pyrimethamine toxicity:
- In case of high dose pyrimethamine or prolonged treatment with low doses, disodium folinate 5 to 50 mg/day should be simultaneously administered, based on the results of the peripheral blood counts.

Method of administration

For intravenous and intramuscular administration only.

For intravenous infusion, disodium folinate may be diluted with 0.9% sodium chloride solution, Hartmann's solution or 5% glucose solution before use. Refer also to sections 6.3 and 6.6.

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.
- Pernicious anaemia or other anaemias due to vitamin B_{12} deficiency.

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

4.4 Special warnings and precautions for use

Disodium folinate should only be given by intramuscular or intravenous injection 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, mecaptopurine, thioguanine). Such macrocytosis should not be treated with folinic acid.

In epileptic patients treated with phenobarbital, phenytoine, primidone, and succinimides there is a risk to increase the frequency of seizures due to a 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 also section 4.5 Interactions).

Disodium folinate / 5-fluorouracil
Disodium folinate may enhance the toxicity risk of 5-fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhoea, which may be dose limiting. When disodium folinate and 5-fluorouracil are used in combination, the 5-fluorouracil dosage has to be reduced more in cases of toxicity than when 5-fluorouracil is used alone.

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-FU 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 dosage of 5-fluorouracil.

Calcium levels should be monitored in patients receiving combined 5-fluorouracil/ folinic acid treatment and calcium supplementation should be provided if calcium levels are low.

Disodium folinate / methotrexate
For specific details on reduction of methotrexate toxicity refer to the SmPC 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 SPC for methotrexate). The presence of preexisting- or methotrexate-induced renal insufficiency is potentially associated with delayed excretion of methotrexate and may increase the need for higher doses or more prolonged use of disodium folinate.

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.

An accidental overdose with a folate antagonist, such as methotrexate, should be treated as a medical emergency. As the time interval between methotrexate administration and folinate rescue increases, disodium folinate effectiveness in counteracting toxicity decreases.

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

This product contains sodium: 5.5 mg/ml Na^+, equivalent with 14.0 mg/ml and 0.24 mmol/ml NaCl, to be taken into consideration by patients on a controlled sodium diet and **in case of** pediatric use.

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.

Disodium folinate may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoine and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed because the hepatic metabolism is increased as folates are one of the cofactors) (see also sections 4.4 and 4.8).
Concomitant administration of disodium folinate with 5-fluorouracil has been shown to enhance the efficacy and toxicity of 5-fluorouracil (see sections 4.2, 4.4 and 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. No formal animal reproductive toxicity studies with disodium folinate have been conducted. There are no indications that folic acid induces harmful effects if administered during pregnancy. During pregnancy, methotrexate should only be administered on strict indications, where the benefits of the drug 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 lactation, there are no limitations as to the use of disodium folinate to diminish toxicity or counteract the effects.

5-fluorouracil use is generally contraindicated during pregnancy and contraindicated during breastfeeding; this applies also to the combined use of disodium folinate with 5-fluorouracil.
Please refer also to the summaries of product characteristics for methotrexate-, other folate antagonists and 5-fluorouracil-containing medicinal products.

Breast-feeding
It is not known whether disodium folinate is excreted into human breast milk. Disodium folinate can be used during breast-feeding when considered necessary according to the therapeutic indications.

4.7 Effects on ability to drive and use machines

There is no evidence that disodium folinate has an effect on the ability to drive or use machines.

4.8 Undesirable effects

The frequencies of adverse events are ranked according to the following:

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)

Both therapeutic indications:

System Organ Class (SOC)	**Frequency**					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Immune system disorders					Allergic reactions, including anaphylactoid/anaphylactic reactions and urticaria	
Psychiatric disorders				Insomnia, agitation and depression after high doses		
Nervous system disorders				Increase in the frequency of attacks in epileptics (see also section 4.5)		
Gastrointestinal disorders				Gastrointestinal disorders after high doses		
General disorders and administration site conditions			Fever has been observed after administration of folinate as solution for injection			

Combination therapy with 5-fluorouracil: Generally, the safety profile depends on the applied regimen of 5-fluorouracil due to enhancement of the 5-fluorouracil induced toxicities:						
System Organ Class (SOC)	**Frequency**					
	Very common	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Metabolism and nutrition disorder						Hyperammonaemia
Blood and lymphatic system disorders	Bone marrow failure, including fatal cases					
General disorders and administration site conditions	Mucositis, including stomatitis and chelitis. Fatalities have occurred as a result of mucositis.					
Skin and subcutaneous tissue disorder		Palmar-Plantar Erythrodys-aesthesia				
Monthly regimen:						
Gastrointestinal disorders	Vomiting and nausea					
No enhancement of other 5-fluorouracil induced toxicities (e.g. neurotoxicity). **Weekly regimen:**						
Gastrointestinal disorders	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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

There have been no reported sequelae in patients who have received significantly more disodium folinate than the recommended dosage. However, excessive amounts of disodium folinate may nullify the chemotherapeutic effect of folic acid antagonists.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Detoxifying agents for antineoplastic treatment; ATC code: V03AF06

Disodium folinate is the sodium salt of 5-formyl tetrahydrofolic acid. It is an active metabolite of folinic acid and an essential coenzyme for nucleic acid synthesis in cytotoxic therapy.

Disodium folinate is frequently used to diminish the toxicity and counteract the action of folate antagonists, such as methotrexate. Disodium folinate and folate antagonists share the same membrane transport carrier and compete for transport into cells, stimulating folate antagonist efflux. It also protects cells from the effects of folate antagonist by repletion of the reduce folate pool. Disodium folinate serves as a pre-reduced source of H4 folate; it can therefore bypass folate antagonist blockage and provide a source for the various coenzyme forms of folic acid.

Disodium folinate is also frequently used in the biochemical modulation of fluorouracil (5-FU) to enhance its cytotoxic activity. 5-FU inhibits thymidylate synthase (TS), a key enzyme involved in pyrimidine biosynthesis, and folinate enhances TS inhibition by increasing the intracellular folate pool, thus stabilising the 5FU-TS complex and increasing activity.

Finally intravenous disodium folinate can be administered for the prevention and treatment of folate deficiency when it cannot be prevented or corrected by the administration of folic acid by the oral route. This may be the case during total parenteral nutrition and severe malabsorption disorders. It is also indicated for the treatment of megaloblastic anaemia due to folic acid deficiency, when oral administration is not feasible.

5.2 Pharmacokinetic properties

Absorption
Following intramuscular administration of the aqueous solution, systemic availability is comparable to an intravenous administration. However, lower peak serum levels (C_{max}) are achieved.

Distribution
The distribution volume of folinic acid is not known.
Peak serum levels of the parent substance (D/L-5-formyl-tetrahydrofolic acid, folinic acid) are reached 10 minutes after i.v. administration.
AUC for L-5-formyl-THF and 5-methyl-THF were 28.4±3.5 mg.min/l and 129±112 mg.min/l after a dose of 25 mg. The inactive D-isomer is present in higher concentration than L-5-formyl-tetrahydrofolate.

Biotransformation
Disodium folinate is a racemate where the L-form (L-5-formyl-tetrahydrofolate, L-5-formyl-THF), is the active enantiomer.
The major metabolic product of folinic acid is 5-methyl-tetrahydrofolic acid (5-methyl-THF) which is predominantly produced in the liver and intestinal mucosa.

Elimination
The elimination half-life is 32 - 35 minutes for the active L-form and 352 - 485 minutes for the inactive D-form, respectively.
The total terminal half-life of the active metabolites is about 6 hours (after intravenous and intramuscular administration).
80-90 % is excreted with the urine (5- and 10-formyl-tetrahydrofolates inactive metabolites), and 5-8 % with the faeces.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium citrate
Sodium hydroxide
Hydrochloric acid diluted
Water for Injections

6.2 Incompatibilities

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

Incompatibilities have been reported between injectable forms of disodium folinate and injectable forms of droperidol, foscarnet and methotrexate.

Droperidol
1. Droperidol 1.25 mg/0.5 ml with (calcium) folinate 5 mg/0.5 ml, immediate precipitation in direct admixture in syringe for 5 minutes at 25° C followed by 8 minutes of centrifugation.
2. Droperidol 2.5 mg/0.5 ml with (calcium) folinate 10 mg/0.5 ml, immediate precipitation when the drugs were injected sequentially into a Y-site without flushing the Y-side arm between injections.

Foscarnet:
Foscarnet 24 mg/ml with Sodium folinate 20 mg/ml formation of a cloudy yellow solution reported.

6.3 Shelf life

Shelf-life as packaged for sale:
3 years.

Shelf-life after dilution:
Chemical and physical in-use stability of the product diluted to 0.5mg/ml with 0.9% Sodium Chloride Intravenous Infusion, 5% glucose Intravenous Infusion or Hartmann's solution in PVC infusion bags (0.5 mg/ml) has been demonstrated for 24 hours at 15-25°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 to 8 °C, unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability of mixtures of disodium folinate with 5-fluorouracil in PVC infusion bags and glass bottles for infusion has been demonstrated for 5 days at 15-25°C. Different proportions of VoriNa 25mg/ml, solution for injection with 5-fluorouracil injection 50 mg/ml have been tested resulting in the following concentrations.

Concentration mg/ml in final mixture	
Disodium folinate	**5-fluorouracil**
16.7	16.7
7.1	35.8
4.6	40.8

From a microbiological point of view, these mixtures 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 8 hours at room temperature (not above 25°C), unless reconstitution/dilution (etc) has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Vials with a nominal volume of 2, 4, 14, 20 and 40 ml colourless glass type 1 (Ph. Eur) with a butylrubber stopper with an inert fluoro-polymeric coating on the inner side and with an aluminum seal covered with a polypropylene snap cap. Trade package quantities: Boxes with one vial of 2, 4, 14, 20 or 40 ml or boxes with 25 vials of 2 ml, or boxes with 10 vials of 4, 14, 20 or 40ml. Individual boxes of one vial in wrap-up seal presented in the following quantities: 10 vials of 2 ml, 3 vials of 14 ml, 15 vials of 14 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

VoriNa 25 mg/ml, solution for injection can be diluted with 0.9% NaCl solution or 5% glucose solution or Hartmann's solution. This medicinal product can be mixed with 5-fluorouracil.

The medicinal product is for single use only. Any unused solution should be discarded.
Prior to administration, disodium folinate should be inspected visually. The solution for injection or infusion should be a clear and yellowish solution. If cloudy in appearance or particles are observed, the solution should be discarded.
Disodium folinate solution for injection or infusion is intended only for single use. Any unused portion of the solution should be disposed of in accordance with the local requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmachemie B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 0937/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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