NEW ZEALAND DATA SHEET

1. PRODUCT NAME

EUROFOLIC 10 mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of EUROFOLIC solution for injection contains 10 mg folinic acid (as calcium folinate 10.8 mg/mL).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- As rescue therapy to reduce toxicity following high-dose methotrexate therapy.
- Has shown good results in the treatment of certain megaloblastic anaemias resulting from folic acid deficiency. This mainly occurs in infants, during pregnancy, in malabsorption syndromes, liver diseases, sprue and malnutrition. It is not more effective than folic acid for these conditions
- Overdosage of methotrexate and in impaired methotrexate elimination
- Reducing the toxicity and circumventing the effect of folic acid antagonists.

4.2 Dose and method of administration

Dose is expressed in units of mg of folinic acid. *(as Calcium folinate potency is usually expressed in terms of equivalent units of folinic acid.)*

EUROFOLIC may be administered by the intramuscular or intravenous route.

EUROFOLIC should not be administered intrathecally.

When required for intravenous infusion, folinic acid may be diluted with either glucose 5% intravenous infusion or sodium chloride 0.9% intravenous infusion to give a final concentration of 0.05 to 0.4 mg/mL. Further diluted solutions of folinic acid in glucose 5% intravenous infusion and sodium chloride 0.9% intravenous infusion are stable for 24 hours when stored between 2ºC to 8ºC.

To avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation.

In the treatment of accidental overdose of folic acid antagonists e.g. methotrexate, folinic acid should be given as soon as possible. As the time interval between antifolate administration and folinic acid rescue increases, folinic acid effectiveness in counteracting toxicity decreases.

Monitoring of serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with folinic acid. Delayed methotrexate excretion may be caused by a third space fluid accumulation (i.e. ascites, pleural effusion), renal insufficiency or inadequate hydration. Under such circumstances, higher doses of folinic acid or prolonged administration may be indicated.

EUROFOLIC contains no antimicrobial agent. The product is for single use in one patient only. Discard any residue.

Admixed solutions for parenteral administration should be visually inspected for particulate matter and discolouration prior to administration where solution and container permit. Do not use if solution is cloudy or precipitated.

Folinic acid should not be mixed in the same infusion as fluorouracil as a precipitate may form.

Laboratory Tests

Patients being treated with folinic acid following methotrexate therapy including inadvertent overdose, or patients with impaired methotrexate elimination should have serum creatinine and methotrexate levels determined at intervals of 24 hours. Folinic acid dosage should be adjusted on the basis of laboratory test results.

Folinic Acid Rescue after High Dose Methotrexate Therapy

The dose of folinic acid required depends on the amount of methotrexate administered and whether there is impaired methotrexate elimination. The following dosing guidelines are for a methotrexate dose of 12 to 15 g/m2 by intravenous infusion over four hours. Folinic acid is commenced 24 hours after the start of the methotrexate infusion.

Normal Methotrexate Elimination

Laboratory findings: Serum methotrexate concentration approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and < 0.2 micromolar at 72 hours.
Folinic acid dose: 15 mg every 6 hours for 60 hours (ten doses).

Delayed Late Methotrexate Elimination
Laboratory findings: Serum methotrexate concentration > 0.2 microM at 72 hours and > 0.05 microM at 96 hours.
Folinic acid dose: 15 mg every six hours until serum methotrexate concentration < 0.05 microM.

Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury
Laboratory findings: Serum methotrexate concentration greater than or equal to 50 microM at 24 hours, or greater than or equal to 5 microM at 48 hours, or greater than or equal to 100% increase in serum creatinine concentration at 24 hours.

Folinic acid dose: 150 mg intravenously every three hours until serum methotrexate concentration < 1 microM, then 15 mg intravenously every three hours until serum methotrexate concentration < 0.05 microM.

Serum creatinine and methotrexate concentrations should be determined at least once daily.

Patients who experience delayed methotrexate elimination are likely to develop reversible renal failure. In addition to folinic acid, these patients require hydration and urinary alkalinisation (pH 7.0 or greater), and close monitoring of fluid and electrolyte status until the serum methotrexate concentration has fallen below 0.05 microM and the renal failure has resolved.

Some patients will have abnormalities in methotrexate elimination or renal function following methotrexate administration which are significant but less severe than the abnormalities described above. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, folinic acid rescue should be extended for an additional 24 hours (total of 14 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other medications which interact with methotrexate (e.g. medications which may interfere with methotrexate elimination or binding to serum albumin) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Note. The above dosage recommendations do not necessarily apply to experimental high dose methotrexate therapy. High dose methotrexate therapy should only be administered by qualified specialists and in hospitals where the necessary facilities are available. Recent published literature should be consulted for details at all times.

Inadvertent Methotrexate Overdose

Folinic acid should begin as soon as possible after inadvertent overdosage of methotrexate. As the time interval between antifolate administration and folinic acid rescue increases, folinic acid's effectiveness in counteracting toxicity diminishes.

The recommended dose is 10 mg/m2 intravenously or intramuscularly every six hours until the serum methotrexate concentration is less than 0.01 microM.

Serum creatinine and methotrexate concentrations should be determined at 24 hour intervals. If the 24 hour serum creatinine concentration has increased 50% over baseline, or the 24 hour methotrexate concentration is greater than 5 microM or the 48 hour concentration greater than 0.9 microM, the dose of folinic acid should be increased to 100 mg/m2 every three hours until the methotrexate concentration is less than 0.01 microM. Hydration (3 L/day) and urinary alkalinisation with sodium bicarbonate solution should be employed concomitantly. The bicarbonate should be adjusted to maintain the urine pH at 7.0 or greater. Foods, drinks and drugs that may increase urinary acidity should be avoided during the therapy.

Treatment of Megaloblastic Anaemias

Parenteral administration: Folinic acid dose up to 1 mg daily. There is no evidence that doses greater than 1 mg/day have greater efficacy than those of 1 mg; additionally, loss of folate in urine becomes roughly logarithmic as the amount administered exceeds 1 mg.

Treatment of Pyrimethamine Overdosage

The dosage of pyrimethamine in treating toxoplasmosis is 10 to 20 times its dosage for malaria and approaches the toxic level. Since folinic acid is not utilised by protozoa, it can be given simultaneously without impairing the effectiveness of therapy. The usual dosage is 3 to 9 mg/day by intramuscular injection for three days or until the platelet and leucocyte counts have reached safe levels.

Special populations

No data are available.

Paediatric population

No data are available.

For instructions on dilution of the medicine before administration, see Section 6.6 Special precautions for disposal.

4.3 Contraindications

Folinic acid should not be used as therapy for pernicious anaemia and other megaloblastic anaemias secondary to cyanocobalamin (vitamin B12) deficiency. When treating these conditions with EUROFOLIC, haematological remission may occur, but neurological manifestations are likely to progress.

Folinic acid should not be used in patients who are hypersensitive to any of the constituents in the preparation.

4.4 Special warnings and precautions for use

Folinic acid should only be used with folic acid antagonists, e.g. methotrexate, or fluoropyrimidines, e.g. 5-fluorouracil, under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic agents.

Because of the calcium ion content of calcium folinate no more than 160 mg of folinic acid (16 mL) should be injected intravenously per minute.

Folinic acid may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving folinic acid and fluorouracil. Concomitant granulocytopenia and fever were present in some, but not all, of the patients.

Seizures and/or syncope have been reported rarely in cancer patients receiving folinic acid usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases. Since three patients had recurrent neurological symptoms on rechallenge with folinic acid, further treatment with folinic acid is not recommended in these circumstances.

Simultaneous therapy with antineoplastic folic acid antagonist (e.g. methotrexate) and folinic acid is not recommended because the effect of the folic acid antagonist is either reduced or completely inhibited.

Folinic acid should be given as soon as possible after accidental methotrexate overdosage because the effectiveness of folinic acid decreases as the time interval between methotrexate and folinic acid administration increases.

Folinic acid has no effect on nonhaematological toxicities of methotrexate, such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Folinic acid is not suitable for the treatment of pernicious anaemias and other anaemias resulting from lack of vitamin B12. Haematological remissions may occur, while the neurological manifestations remain progressive.

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.

Because of the Ca2+ content of the folinic acid injections, no more than 16 mL of the 10 mg/mL formulations (160 mg of folinic acid) should be injected intravenously per minute.

In epileptic patients treated with phenobarbital, phenytoin, 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 folinic acid administration and after discontinuation is recommended. (see also Section 4.5 Interactions with other medicines and other forms of interactions).

Combination therapy with 5-fluorouracil

Folinic acid enhances the toxicity 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. In addition, hematological adverse reactions have been observed. When these drugs

are administered concurrently in the palliative therapy of advanced colorectal cancer, the dosage of 5-fluorouracil should be reduced accordingly.

Although the toxicities observed in patients treated with the combination of folinic acid followed by 5-fluorouracil are qualitatively similar to those observed in patients treated with 5-fluorouracil alone, gastrointestinal toxicities (particularly stomatitis and diarrhoea) are observed more commonly, may be more severe and of prolonged duration in patients treated with the combination.

Combination therapy with folinic acid/5-fluorouracil must not be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have completely resolved. Patients with diarrhoea must be monitored with particular care until the diarrhoea has resolved, as rapid clinical deterioration leading to death can occur. 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.

Particular care should be taken when treating elderly or debilitated colorectal cancer patients with folinic acid/5-fluorouracil, as these patients may be at increased risk of severe toxicity, particularly severe gastrointestinal toxicity.

In elderly patients and patients who have undergone preliminary radiotherapy, it is recommended to begin with a reduced dosage of 5-fluorouracil.

Folinic acid must not be mixed with 5-fluorouracil in the same intravenous injection or infusion.

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.

Laboratory tests – Combination therapy with 5-fluorouracil

Patients being treated with folinic acid/5-fluorouracil combination should have a CBC with differential and platelets prior to each treatment. During the first two courses of a CBC with differential and platelets has to be repeated weekly and thereafter, once each cycle at the time of anticipated WBC nadir. Electrolytes and liver function tests should be performed propr to each treatment for the first

three cycles then prior to every other cycle. Dosage modifications of 5-fluorouracil should be instituted as follows, based on the most severe toxicities:

Diarrhoea and/or Stomatitis	WBC/mm^3 Nadir	Platelets/mm^3 Nadir	5-FU dose
Moderate	1,000-1.900	25-75,000	decrease 20%
Severe	< 1,000	< 25,000	decrease 30%

If no toxicity occurs, the 5-fluouracil dose may be increased 10%. Treatment should be deferred until WBC's are 4,000/mm3. If blood counts do not reach these levels within two weeks, treatment should be discontinued. Patients should be followed up with physical examination prior to each treatment course and appropriate radiological examination as needed. Treatment should be discontinued when there is clear evidence of tumour progression.

Folinic acid/methotrexate

For specific details on reduction of methotrexate toxicity refer to the SPC of methotrexate.

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 folinic acid rescue increases, folinic acid effectiveness in counteracting toxicity decreases.

Folinic acid 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 health-care professional labeling 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 folinic acid.

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

Laboratory tests

5-FU/folinic acid therapy

Complete blood count (CBC) with differential and platelets: prior to each treatment; weekly during the first two courses; at time of anticipated white blood cell (WBC) nadir in all courses thereafter.

Electrolytes and liver function tests: prior to each treatment for the first three courses and prior to every other course thereafter.

Methotrexate/folinic acid therapy

Serum creatinine levels and serum methotrexate levels: at least once daily.

Urine pH: in cases of methotrexate overdose or delayed excretion, monitor as appropriate, to ensure maintenance of pH ≥7.0.

4.5 Interaction with other medicines and other forms of interaction

Folic acid in large amounts may counteract the antiepileptic effect of cotrimoxazole, methotrexate, phenobarbitone, phenytoin and primidone, and increase the frequency of seizures in susceptible children (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 Special warnings and precautions for use and 4.8 Undesirable effects). High oral, intravenous or intramuscular doses of folinic acid may reduce the efficacy of intrathecally administered methotrexate.

Folinic acid may enhance the toxicity of fluoropyrimidines e.g. 5-fluorouracil (See Section 4.4 Special warnings and precautions for use).

High doses of folinic acid may reduce the efficacy of intrathecally administered methotrexate.

Concurrent administration of chloramphenicol and folinic acid in folate deficient patients may result in antagonism of haematopoietic response to folic acid.

4.6 Fertility, pregnancy and lactation

Effects on fertility

No data available.

Use in pregnancy

Category A

Folinic acid has been taken by a large number of pregnant women and women of childbearing potential without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed. However caution is essential in the use of folinic acid in pregnant women as the safety of folinic acid in pregnancy has not been established. During pregnancy, 5-fluorouracil and 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 fetus. Should treatment with methotrexate or other folate antagonists take place despite pregnancy or lactation, there are no limitations as to the use of folinic acid to diminish toxicity or counteract the effects.

Use in lactation

As it is not known whether folinic acid is excreted in milk, caution should be exercised when folinic acid is administered to breastfeeding mothers.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse reactions to folinic acid are rare. Occasional hypersensitivity reactions have been reported; pyrexia, urticaria, hypersensitivity, anaphylatic shock and anaphylactic reactions have occurred after parenteral administration. Nausea and vomiting with very high doses of folinic acid have been reported. Seizures and/or syncope have been reported rarely in cancer patients receiving folinic acid, usually in association with fluoropyrimidine administration (see Section 4.4 Special warnings and precautions for use).

Cases of Steven-Johnson Syndrome (SJS) and Toxic Epidermal necrolysis (TEN), some fatal, have been reported in patients receiving EUROFOLIC in combination with other agents known to be associated with these disorders. A contributory role of EUROFOLIC in these occurrences of SJS/TEN cannot be excluded.

Generally, the safety profile depends on the applied regimen of 5-fluorouracil due to enhancement of the 5-fluorouracil induced toxicities. Additional undesirable effects when used in combination with 5-fluouracil are presented in the table below:

Table 1. Adverse Drug Reactions folinic acid – Combination therapy

System Organ Class	ADR term
Blood and lymphatic system disorders	Leucopenia Neutropenia Thrombocytopenia Anaemia
Metabolism and nutrition disorders	Hyperammonaemia
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Stomatitis
Skin and subcutaneous tissue disorders	Palmar-plantar Erythrodysaesthesia symdrome (hand-foot syndrome)
General disorders and administration site conditions	Mucosal inflammation

Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhoea) and myelosuppression. In patients with diarrhoea, rapid clinical deterioration leading to death can occur.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Folinic acid is an intermediate in the metabolism of folic acid and can therefore be considered as a naturally occurring substance. Large doses have been administered with no apparent adverse effects. Such doses suggest that administration of this drug is relatively safe. Signs of excessive dosing, if they occur, should be treated symptomatically.

Excessive amounts of folinic acid may nullify the chemotherapeutic effect of folic acid antagonists. Should overdosage of the combination of 5-fluorouracil and folinic acid occur, the overdosage instructions for 5-fluorouracil should be followed.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The structural formula of calcium folinate is

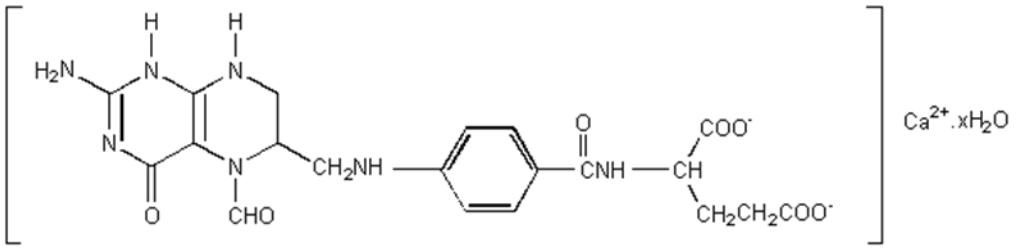

Figure 1. Chemical structure of calcium folinate.

Molecular formula: C20H21CaN7O7

Molecular weight: 511.5

CAS: 1492-18-8

Calcium folinate is a white or light yellow, amorphous or crystalline powder, sparingly soluble in water and practically insoluble in acetone and ethanol. Calcium folinate potency is usually expressed in terms of equivalent units of folinic acid.

Pharmacotherapeutic group

All other therapeutic products, detoxifying agents for antineoplastic treatment

ATC code: V03AF03

Mechanism of action

Folinic acid is the formyl derivative of tetrahydrofolic acid (THF) which is a metabolite and active form of folic acid. It is effective in the treatment of megaloblastic anaemia caused by folic acid deficiency and is a potent antidote for both the haematopoietic and reticuloendothelial toxic effects of folic acid antagonists, e.g. methotrexate, pyrimethamine, trimethoprim. In some cancers, folinic acid enters

and 'rescues' normal cells, in preference to tumour cells, from the toxic effects of folic acid antagonists, due to a difference in membrane transport mechanism. This principle is applied in high dose methotrexate therapy with 'folinic acid rescue'.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Following administration, calcium folinate enters the body's pool of reduced folates. Peak levels of total reduced folates are reached on average 10 minutes and 52 minutes following intravenous and intramuscular administration, respectively. It has been reported that peak plasma levels of folinic acid are achieved 10 minutes and 28 minutes after intravenous and intramuscular administration, respectively. Calcium folinate is rapidly converted in vivo to 5- methyl tetrahydrofolate (5-methyl-THF), the active metabolite. 5-methyl-THF becomes the major circulating form of the drug. Peak levels of 5-methyl-THF are observed at 1.3 and 2.8 hours following intravenous and intramuscular administration.

Folates are distributed to all tissues and concentrated in the liver with moderate amounts found in the cerebrospinal fluid. Following intravenous or intramuscular administration of 25mg of folinic acid the half life for total reduced folates has been reported to be 6.2 hours. Folinic acid is mainly eliminated as 10-formyl tetrahydrofolate and 5,10–methyl tetrahydrofolate with the metabolites mainly excreted in the urine (approx 80-90%). Elimination is logarithmic in doses exceeding 1 mg.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of this Data Sheet.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride 8 mg/mL

Sodium hydroxide

Water for injections

Nitrogen as protective gas.

6.2 Incompatibilities

Folinic acid has been reported to be incompatible with injectable forms of methotrexate, fluorouracil, droperidol, phosphonosulphate and foscarnet and sodium bicarbonate.

6.3 Shelf life

The shelf life is 30 months from the date of manufacturing when stored in the unopened container. This medication should not be used after the expiration date.

The chemical and physical in-use stability of the solution diluted with Sodium Chloride 0.9% or Glucose 5% for intravenous infusion has been demonstrated for 24 hours at a temperature not exceeding 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 dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Keep the container in the outer carton in order to protect from light.

Store in a refrigerator (2 °C – 8 °C).
Keep this medicine out of the sight and reach of children.

6.5 Nature and contents of container

Amber glass vials (Type I glass); Stoppers (bromobutyl rubber) with aluminum "flip-off" seal for 5, 10, 35, 50 or 100 ml solution.

50 mg in 5 mL amber glass vial x 1
100 mg in 10 mL amber glass vial x 1
350 mg in 35 mL amber glass vial x 1
500 mg in 50 mL amber glass vial x 1
1000 mg in 100 mL amber glass vial x 1

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

EUROFOLIC should be visually inspected before use. The solution for injection or infusion should be a clear and yellowish solution. If cloudiness or particles are observed, the solution should be discarded.

EUROFOLIC 10 mg/ml 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. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

ORSPEC Pharma Management Limited
PO BOX 59013
Mangere Bridge
Auckland 2151
Tel: +6421 054 3923

9. DATE OF FIRST APPROVAL

11 November 2025

10. DATE OF REVISION OF THE TEXT

SUMMARY TABLE OF CHANGES