NEW ZEALAND DATA SHEET

1 PRODUCT NAME

CALCIUM FOLINATE SANDOZ 10mg/mL; concentrate for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Calcium Folinate Sandoz, concentrate for injection contains 10 mg folinic acid (as calcium folinate 10.8mg/mL).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate 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.)

Calcium Folinate Sandoz may be administered by the intramuscular or intravenous route.

Calcium Folinate Sandoz 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.

Calcium Folinate Sandoz 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 alkalisation with sodium bicarbonate solution should be employed concomitantly. The bicarbonate should be adjusted to maintain the urine pH at 7.0 or greater.

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.
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 Calcium Folate Sandoz, 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 160mg of folinic acid (16mL) 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.

4.5 Interaction with other medicines and other forms of interaction

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin and primidone, and increase the frequency of seizures in susceptible children.

Folinic acid may enhance the toxicity of fluoropyrimidines e.g. 5-fluorouracil (See Precautions).

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

4.6 Fertility, pregnancy and lactation

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.

**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

Reporting suspected adverse reaction 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://nzphvc.otago.ac.nz/reporting/](https://nzphvc.otago.ac.nz/reporting/)

Adverse reactions to folinic acid are rare. Occasional hypersensitivity reactions have been reported; pyrexia, urticaria and anaphylactoid 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 Precautions).

### 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.

Contact the Poisons Information Centre on (telephone 0800 POISON or 0800 764766) for advice on management of overdose.

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### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

The structural formula of calcium folinate is:

\[
\text{Molecular formula: } C_{20}H_{21}CaN_7O_7
\]

![Structural formula of calcium folinate](image)

Molar mass = 511.5 (anhydrous calcium salt)

Molecular formula: \(C_{20}H_{21}CaN_7O_7\)
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**

**PHARMACOLOGY**

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'.

5.2 **Pharmacokinetic properties**

Pharmacokinetics

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.

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**6 PHARMACEUTICAL PARTICULARS**

6.1 **List of excipients**

Sodium chloride (8mg/mL)

Water for Injections.
6.2 Incompatibilities
Folinic acid has been reported to be incompatible with droperidol injection and foscarnet injection and sodium bicarbonate.

6.3 Shelf life
2 years
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
Store at 2 – 8°C. (Refrigerate. Do not freeze). Protect from light.

6.5 Nature and contents of container
30mg in 3mL amber glass vial x 1
50mg in 5mL amber glass vial x 1
100mg in 10mL amber glass vial x 1
200mg in 20mL amber glass vial x 1
350mg in 35mL amber glass vial x 1
500mg in 50mL amber glass vial x 1
1000mg in 100mL amber glass vial x 1
Each vial has a fluoropolymer-coated chlorobutyl rubber stopper with aluminium cap.
Not all pack sizes may be marketed.

6.6 Special precautions for handling, reconstitution and disposal
Prior to administration, Calcium Folinate Sandoz should be inspected visually. The solution for injection or infusion should be a clear yellowish solution. If cloudy in appearance or particles are observed, the solution should be discarded. Calcium Folinate Sandoz solution for injection or infusion is intended for single use only. Any unused portion of the solution should be disposed of in accordance with the local requirements.

7 MEDICINE SCHEDULE

Prescription Medicine
8 SPONSOR

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Telephone: 0800 354 335

9 DATE OF FIRST APPROVAL

07/12/2017

10 DATE OF REVISION OF THE TEXT

17 November 2017