

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Leucovorin Calcium 15 mg Tablet.

DBL™ Leucovorin Calcium 15 mg/2 mL, 50 mg/5 mL or 300 mg/30 mL Solution for Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DBL Leucovorin Calcium Tablet contains 15 mg folic acid (as calcium folinate*).

Each 2 mL ampoule of DBL Leucovorin Calcium Solution for Injection contains 7.5 mg/mL folic acid (as calcium folinate*).

Each 5 mL vial of DBL Leucovorin Calcium Solution for Injection contains 10 mg/mL folic acid (as calcium folinate*).

Each 30 mL ampoule of DBL Leucovorin Calcium Solution for Injection contains 10 mg/mL folic acid/mL (as calcium folinate*).

*Calcium folinate is also known as calcium folinate hydrate.

Excipients with known effect:

Solution for Injection

Each 2 mL ampoule of DBL Leucovorin Calcium Injection contains 8.1 mg/mL of sodium chloride.

Each vial of DBL Leucovorin Calcium Injection 50 mg/5 mL and 300 mg/30 mL contains 8.5 mg/mL of sodium chloride.

Tablets

Each DBL Leucovorin Calcium Tablet contains 141.4 mg of lactose monohydrate.

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

3. PHARMACEUTICAL FORM

Tablets

DBL Leucovorin tablets are light yellow, round, flat, scored, uncoated tablet, engraved with CF. .

Solution for Injection

DBL™ Leucovorin Calcium Injection is a sterile, clear, straw to pale yellow coloured solution, free from visible particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL Leucovorin Calcium 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.

DBL Leucovorin Calcium also has shown good results in reducing the toxicity and circumventing the effect of folic acid antagonists, if therapeutically desired.

Use in combination with 5-fluorouracil in the treatment of advanced colorectal carcinoma.

4.2 Dose and method of administration

Dose

Antidote following methotrexate therapy, impaired methotrexate elimination or inadvertent overdosage

In the treatment of accidental overdosage of folic acid antagonists, e.g., methotrexate (MTX), DBL Leucovorin Calcium should be administered as promptly as possible and within 24 hours after the beginning of methotrexate infusion. As the time interval between antifolate administration and DBL Leucovorin Calcium rescue increases, DBL Leucovorin Calcium's effectiveness in counteracting toxicity diminishes.

The recommendations for rescue are based on a methotrexate dose of 12-15 g/m² administered by intravenous infusion over 4 hours (see methotrexate Data Sheet for full prescribing information). Rescue starts 24 hours after the beginning of the methotrexate infusion at a dose of 15 mg (approximately 10 mg/m²) every 6 hours for 10 doses. In the presence of gastrointestinal toxicity, nausea or vomiting, DBL Leucovorin Calcium should be administered parenterally.

To avoid discomfort to patients from multiple injections, oral tablets may be given for 24 hours after the initial rescue parenteral injection. A complete oral rescue is also possible and has been used by some authors. Patients with malabsorption syndromes or other gastrointestinal disturbances such as vomiting and diarrhoea should not be treated orally.

In addition to calcium folinate administration, measures to ensure the prompt excretion of methotrexate are an integral part of the calcium folinate rescue. These measures include:

- Monitoring of serum MTX concentration is essential in determining the optimal dose and duration of treatment with DBL Leucovorin Calcium. Serum creatinine and methotrexate levels should be determined at least once daily.
- Administration, hydration (3 L/day) and urinary alkalinisation (with bicarbonate and/or acetazolamide) to pH of 7.0 or greater should be continued until the methotrexate level is below 0.05 micromolar. The dose should be adjusted or rescue extended based on guidelines provided in the table below.

Delayed MTX 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 DBL Leucovorin Calcium or prolonged administration may be indicated. Doses higher than those recommended for oral use must be given intravenously.

Patients who experience delayed methotrexate elimination are likely to develop reversible renal failure. These patients require continuing hydration, urinary alkalinisation and close monitoring of fluid and electrolyte status, until the serum methotrexate level has fallen to below 0.05 micromolar 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. If these abnormalities are associated with significant clinical toxicity, Calcium folinate 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 considered when laboratory abnormalities or clinical toxicities are observed.

Guidelines for dosage and administration for calcium folinate rescue

Clinical Situation	Laboratory Findings	Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 μM at 48 hours, and less than 0.2 μM at 72 hours.	15 mg PO, IM or IV q6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Methotrexate Elimination	Serum methotrexate level remaining above 0.2 μM at 72 hours, and more than 0.05 μM at 96 hours after administration.	Continue 15 mg PO, IM or IV q6 hours, until methotrexate level is less than 0.05 μM .

Treatment of pyrimethamine overdose

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

Treatment of megaloblastic anaemias

Parenteral administration

Up to 1 mg DBL Leucovorin Calcium Solution for Injection daily. Larger dosages do not increase the effect because folate excretion in urine increases roughly logarithmically as the dosage is increased above 1 mg.

Oral administration

Daily doses of 5 mg to 15 mg of DBL Leucovorin Calcium Tablets

5-Fluorouracil/DBL Leucovorin Calcium therapy for treatment of advanced colorectal carcinoma

Various combination regimens have been studied. Based on available clinical evidence, the following regimen has been found to be effective in advanced colorectal carcinoma: DBL Leucovorin Calcium given at a dose of 200 mg/m² by intravenous injection, followed immediately by 5-fluorouracil at an initial dose of 370 mg/m² by intravenous injection. This treatment is repeated daily for 5 consecutive days. Subsequent courses may be given after a treatment-free interval of 21-28 days for 2 courses and then repeated at 28-35 day intervals provided the patient has fully recovered from the toxic effects of the prior treatment course.

In subsequent treatment courses, the dosage of 5-fluorouracil should be adjusted based on patient tolerance of the prior treatment course. The daily dosage of 5-fluorouracil should be reduced by 20% for patients who experienced moderate haematologic and gastrointestinal toxicity in the prior treatment course, and by 30% for patients who experienced severe toxicity (see section 4.4 Special warnings and precautions for use). For patients who experienced no toxicity in the prior treatment course, 5-fluorouracil dosage may be increased by 10%. DBL Leucovorin Calcium dosages are not adjusted for toxicity.

Patient monitoring

Patients being treated with the DBL Leucovorin Calcium/5-fluorouracil combination should have a CBC with differential and platelets prior to each treatment. During the first two courses 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 prior 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/mm³ Nadir	Platelets/mm³ 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-fluorouracil 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.

Method of administration

Tablets

DBL Leucovorin Calcium tablets may be administered orally. Oral doses should be taken on an empty stomach or in the fasting state since studies of bioavailability of oral tablets have been done on fasting patients only. Because absorption is saturable, oral administration of doses greater than 25 mg is not recommended.

Solution for Injection

DBL Leucovorin Calcium injection 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.

Because of the Ca²⁺ content of the DBL Leucovorin Calcium injection, no more than 16 mL of the 10 mg/mL formulation (160 mg of DBL Leucovorin Calcium) should be injected intravenously per minute.

DBL Leucovorin Calcium Injection contains no antimicrobial agent. This product is for single use in one patient only.

When required for intravenous infusion, DBL Leucovorin Calcium Injection may be diluted in 1 litre of 5% w/v glucose solution or 0.9% sodium chloride solution. The diluted solutions are stable for 24 hours when stored between 2 to 8°C. However, to avoid microbial contamination hazards, infusion should be commenced as soon as practicable after preparation of the solution. Infusion should be completed within 24 hours and any unused solution should be discarded.

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.

DBL Leucovorin Calcium should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.

4.3 Contraindications

DBL Leucovorin Calcium is contraindicated in patient with:

- Pernicious anaemia and other megaloblastic anaemias secondary to the lack of Vitamin B₁₂. When treating these conditions with DBL Leucovorin Calcium, haematological remission may occur, but neurological manifestations are likely to progress.
- Known hypersensitivity to calcium folinate or to any of the excipients.

Please refer also to the Data Sheet for methotrexate, other folate antagonists and 5-fluorouracil containing medicinal products.

4.4 Special warnings and precautions for use

DBL Leucovorin Calcium Injection 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

Simultaneous therapy with a folic acid antagonist and DBL Leucovorin Calcium is not recommended because the effect of the folic acid antagonist is either reduced or completely inhibited.

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.

Seizures and/or syncope have been reported rarely in cancer patients receiving DBL Leucovorin Calcium, usually in association with fluoropyrimidine administration, and most

commonly in those with CNS metastases. Since three patients had recurrent neurological symptoms on rechallenge with DBL Leucovorin Calcium, further treatment with DBL Leucovorin Calcium is not recommended in these circumstances.

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the DBL Leucovorin Calcium.

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

DBL Leucovorin Calcium 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.

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 calcium folinate administration and after discontinuation is recommended (see also Section 4.5 Interactions with other medicines and other forms of medicines).

Combination therapy with 5-fluorouracil

DBL Leucovorin Calcium 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, haematological adverse reactions have been observed. When DBL Leucovorin Calcium and 5-fluorouracil are used in combination, a lower dose of 5-fluorouracil should be considered in cases of toxicity than when 5-fluorouracil is used alone. .

Combination therapy with DBL Leucovorin Calcium/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.

As diarrhoea may be a sign of gastrointestinal toxicity, patients presenting with diarrhoea must be monitored with particular care until the diarrhoea has resolved since 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.

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

Calcium folinate 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/calcium folinate treatment and calcium supplementation should be provided if calcium levels are low.

Calcium folinate/methotrexate

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

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 calcium folinate rescue increases, calcium folinate effectiveness in counteracting toxicity decreases.

Calcium 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 health-care professional labelling for methotrexate). The presence of pre-existing- 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 calcium folinate.

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

Use in the elderly

Elderly patients are at increased risk of severe toxicity when receiving combination therapy of calcium folinate and fluorouracil. Particular care should be taken when treating these patients.

Paediatric use

There are no data available on use in children.

4.5 Interaction with other medicines and other forms of interaction

When calcium folinate is given in conjunction with a folic acid antagonist (e.g., cotrimoxazole, pyrimethamine, methotrexate, antibiotic with antifolic effect) the efficacy of the folic acid antagonist may either be reduced or completely neutralised.

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin, succinimides and primidone and 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). Also see Sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (undesirable effects). High oral, intravenous or intramuscular doses of DBL Leucovorin Calcium may reduce the efficacy of intrathecally administered methotrexate.

DBL Leucovorin Calcium may enhance the toxicity of fluorouracil (see Section 4.4 Special warnings and precautions for use).

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

4.6 Fertility, pregnancy and lactation

Fertility

No fertility studies have been conducted with calcium folinate in animals.

Pregnancy - Category A.

There are no adequate and well-controlled clinical studies conducted in pregnant or breast-feeding women. No formal animal reproductive toxicity studies with calcium folinate have been conducted. 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 calcium folinate to diminish toxicity or counteract the effects.

5-fluorouracil use is generally contraindicated during pregnancy and lactation; this applies also to the use DBL Leucovorin Calcium combined with 5-fluorouracil.

Please refer also to the Data Sheet for methotrexate, other folate antagonists and 5-fluorouracil-containing medicinal products.

Lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when DBL Leucovorin Calcium is administered to a nursing mother.

DBL Leucovorin Calcium in combination with 5-fluorouracil is not recommended for use in women who are breast-feeding.

4.7 Effects on ability to drive and use machines

DBL Leucovorin Calcium is presumed to be safe since it is unlikely to produce an effect that may impair the patient's ability to concentrate and react and therefore not constitute a risk in the ability to drive and use machines.

4.8 Undesirable effects

Adverse Drug Reactions Leucovorin Calcium - Monotherapy	
System Organ Class	ADR Term
Immune system disorders	Hypersensitivity Anaphylactic reaction Anaphylactic shock
Psychiatric disorders	Insomnia, agitation and depression after high doses.
Nervous system disorders	Increase in the frequency of attacks in epileptic patients (also see Section 4.5 Interactions with medicines and other types of interactions) Seizure Syncope

Skin and subcutaneous tissue disorders	Urticaria
General disorders and administration site conditions	Pyrexia

Cases of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), some fatal, have been reported in patients receiving leucovorin in combination with other agents known to be associated with these disorders. A contributory role of leucovorin 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-fluorouracil are presented in table below.

Adverse Drug Reactions Leucovorin Calcium - Combination Therapy	
System Organ Class	ADR Term
Blood and lymphatic system disorders	Leukopenia Neutropenia Thrombocytopenia Anaemia
Metabolism and nutrition disorders	Hyperammonaemia
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Stomatitis Cheilitis
Skin and subcutaneous tissue disorders	Palmar-plantar Erythrodysesthesia syndrome (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 of suspected adverse reactions

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://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Excessive amounts of leucovorin may nullify the chemotherapeutic effect of folic acid antagonists. Should overdosage of the combination of 5-fluorouracil and calcium folinate occur, the overdosage instructions for 5-FU 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

Mechanism of action

Folinic acid is the formyl derivative of folic acid. When treating megaloblastic anaemias, the results are comparable to those obtained with folic acid. Following an overdose of folic acid antagonists, DBL Leucovorin Calcium performs considerably better than folic acid because the folic acid antagonists inhibit the metabolism of folic acid into folinic acid, but have no effect on the folinic acid.

5.2 Pharmacokinetic properties

Absorption

Calcium folinate is rapidly absorbed in the gastrointestinal tract after oral administration. The oral absorption of calcium folinate is saturable at doses above 25 mg. The bioavailability of calcium folinate is 97% for 25 mg, 75% for 50 mg, and 37% for 100 mg. 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

Tetrahydrofolic acid and its derivatives are distributed to all body tissues, being concentrated in the liver and found in moderate amounts in the CSF. Following a 15 mg dose given either orally or intramuscularly, peak serum folate concentrations of 0.268 micrograms/mL and 0.241 micrograms/mL were detected.

Peak serum levels of the parent substance (D/L-5-formyl-tetrahydrofolinic acid, folinic acid) are reached 10 minutes after intravenous administration and 28 minutes after intramuscular administration.

AUC for L-5-formyl-THF and 5-methyl-THF were 28.4 ± 3.5 mg/min/L and 129 ± 12 mg/min/L after a dose of 25 mg intravenous administration. The inactive D-isomer is present in higher concentration than L-5 formyltetrahydrofolate. Folate is concentrated in the cerebrospinal fluid, although distribution occurs to all body tissues.

Biotransformation

Calcium 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. Calcium folinate is rapidly and extensively converted to 5-methyl tetrahydrofolate (an active metabolite) *in vivo*, with less extensive conversion resulting from parenteral, as opposed to oral, administration.

Peak levels of 5-methyl-THF are observed at 1.3 and 2.8 hours following intravenous and intramuscular administration, respectively. The terminal half-life for total reduced folates is reported as 6.4 hours.

Elimination

Folinic acid is eliminated mainly as 10-formyl tetrahydrofolate and 5,10-methyl tetrahydrofolate. 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). The 5- and 10-formyl-tetrahydrofolates inactive metabolites are mainly excreted via the urine (80-90%), with elimination being logarithmic in with elimination being logarithmic in doses exceeding 1 mg, 5-8% with the faeces.

5.3 Preclinical safety data

Genotoxicity

Genotoxicity studies have not been conducted with calcium folinate. .

Carcinogenicity

Carcinogenicity studies have not been conducted with calcium folinate. .

Reproductive and developmental toxicity

Embryo-fetal reproduction toxicity studies have been performed in rats and rabbits. Rats were dosed up to 1800 mg/m² which is 9 times the maximum recommended human dose, and rabbits were dosed up to 3300 mg/m² which is 16 times the maximum recommended human dose. There was no embryo-fetal toxicity noted in rabbits. At the maximum dose in rats, there was a slight increase in early embryonic resorptions and no other adverse effects on embryo-fetal development. No resorptions were noted in dose groups at 5 times the maximum recommended human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet

Lactose monohydrate, Microcrystalline cellulose, Magnesium stearate.

Solution for Injection

Sodium chloride, Water for Injections.

6.2 Incompatibilities

Leucovorin calcium injection has been reported to be incompatible with injectable forms of methotrexate, 5-fluorouracil, fosacarenet and droperidol and phosphonosulphate.

For more information refer to 'Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 Shelf life

Solution for Injection

24 months.

Tablets

36 months.

6.4 Special precautions for storage

Solution for Injection

Store at 2 to 8°C. Refrigerate. Do not freeze. Protect from light.

Tablets

Store below 25°C.

6.5 Nature and contents of container

Tablets

DBL Leucovorin Calcium tablets are supplied in HDPE bottles of 10 tablets.

Solution for Injection

DBL Leucovorin Calcium 15 mg/2 mL Solution for Injection is packaged in 2 mL amber, Type I glass ampoules in packs of 5 ampoules.

DBL Leucovorin Calcium 50 mg/25 mL Solution for Injection is packaged in 5 mL Type I glass vials with a chlorobutyl rubber stopper in packs of 1 vial.

DBL Leucovorin Calcium 300 mg/30 mL Solution for Injection is packaged in 30 mL Type I glass vials with a chlorobutyl rubber stopper in packs of 1 vial.

*Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Solution for Injection

Prescription Medicine.

Tablets

Pharmacy Only Medicine.

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

Tablets

15 mg: 19 March 1987.

Solution for injection

15 mg/2 mL and 50 mg/5 mL: 29 July 1982.

300 mg/30 mL: 24 November 1998.

10. DATE OF REVISION OF THE TEXT

08 October 2021.

Summary table of changes

Section changed	Summary of new information
All	Minor editorial change for better alignment with the new Data Sheet template
1, 2, 3, 6	Minor editorial change. Product description, dosage form and qualitative and quantitative composition are updated to align with TPDR
4.2 and 4.4	Minor editorial changes. Reformatted to improve readability
4.3, 4.6	Addition of warning that combination of calcium folinate and - fluorouracil use is contraindicated in pregnancy and lactation.
5.2	Update to pharmacokinetic data
5.3	Addition of new embryo-fetal reproduction toxicity data.
4.8	Psychiatric disorders, Nervous system disorders, Gastrointestinal disorders added as new adverse events.