

# NEW ZEALAND DATA SHEET

## 1. PRODUCT NAME

DBL™ Leucovorin Calcium, Solution for Injection, 15 mg/2 mL

DBL™ Leucovorin Calcium, Solution for Injection, 50 mg/5 mL

DBL™ Leucovorin Calcium, Solution for Injection, 300 mg/30 mL

DBL™ Leucovorin Calcium, Tablet, 15 mg

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DBL™ Leucovorin Calcium Injection is a sterile solution of folinic acid (as calcium salt): ampoule (15 mg/2 mL) and vial (50 mg/5 mL).

DBL™ Leucovorin Calcium Tablets contain calcium folinate equivalent to 15 mg folinic acid.

### Excipients with known effect:

*Injection:* Sodium chloride

*Tablet:* Lactose monohydrate

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection: ampoules and vials.

Tablets.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Calcium Leucovorin 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. Calcium Leucovorin 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

Calcium Leucovorin may be given orally or parenterally by intravenous infusion or by intramuscular injection. Calcium Leucovorin should not be administered intrathecally.

## **Parenteral**

Calcium Leucovorin may be diluted for infusion with physiological saline solution. Caution: contains no preservative. If intended for multiple dose use, reconstitute with bacteriostatic water for injection containing benzyl alcohol. The pH of the solution is approximately 7.5. Reconstituted solutions should not be kept for more than 3 days and should be stored below 8°C.

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

## **Oral**

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.

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

Monitoring of serum MTX concentration is essential in determining the optimal dose and duration of treatment with Calcium Leucovorin.

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

## **Laboratory Tests**

Patients being treated with Calcium Leucovorin following methotrexate therapy, including inadvertent overdose, or impaired methotrexate elimination should have serum creatinine and methotrexate levels determined at 24 hour intervals. Calcium Leucovorin dosage should be adjusted based on laboratory test results.

### **As an antidote following methotrexate therapy**

The recommendations for Calcium Leucovorin rescue are based on a methotrexate dose of 12-15 grams/m<sup>2</sup> administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information). Calcium Leucovorin rescue starts 24 hours after the beginning of the methotrexate infusion at a dose of 15 mg (approximately 10 mg/m<sup>2</sup>) every 6 hours for 10 doses.

In the presence of gastrointestinal toxicity, nausea or vomiting, Calcium Leucovorin should be administered parenterally.

Most investigators have successfully used doses of 6-25 mg per dose, repeated at 6 hourly intervals for up to 6-12 doses. Goldie and Price have applied up to a total of 2 grams Calcium Leucovorin in 6 fractions, which is the maximum dose recommended.

To avoid discomfort to patients from multiple injections, Calcium Leucovorin oral tablets may be given for 24 hours after the initial Calcium Leucovorin-Rescue parenteral injection. A complete oral Calcium Leucovorin-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.

Serum creatinine and methotrexate levels should be determined at least once daily. Calcium Leucovorin 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  $5 \times 10^{-8}$  M (0.05 micromolar). The Calcium Leucovorin dose should be adjusted or Calcium Leucovorin rescue extended based on the following guidelines:

### Guidelines for calcium leucovorin dosage and administration

Clinical Situation	Laboratory Findings	Calcium Leucovorin Dosage and Duration
Normal Methotrexate Elimination	Serum methotrexate level approximately 10 micromolar at 24 hours after administration, 1 micromolar at 48 hours, and less than 0.2 micromolar 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 micromolar at 72 hours, and more than 0.05 micromolar at 96 hours after administration.	Continue 15 mg PO, IM or IV q6 hours, until methotrexate level is less than 0.05 micromolar.

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 Leucovorin 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.

### Impaired methotrexate elimination or inadvertent overdose

Calcium Leucovorin rescue should begin as soon as possible after an inadvertent overdose and within 24 hours of methotrexate administration when there is delayed excretion. Calcium Leucovorin  $10 \text{ mg/m}^2$  should be administered IV, IM or PO every 6 hours until the serum methotrexate level is less than  $10^{-8}$ M. Serum creatinine and methotrexate levels should be determined at 24 hour intervals. If the 24 hours serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than  $5 \times 10^{-6}$ M or the 48 hour level is

greater than  $9 \times 10^{-7}M$ , the dose of Calcium Leucovorin should be increased to  $100 \text{ mg/m}^2$  IV every 3 hours until the methotrexate level is less than  $10^{-8}M$ .

Hydration (3 L/d) and urinary alkalinisation with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose 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.

Note: 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.

### **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 Calcium Leucovorin 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 Calcium Leucovorin 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 Calcium Leucovorin.

### **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: Calcium Leucovorin given at a dose of  $200 \text{ mg/m}^2$  by intravenous injection, followed immediately by 5-fluorouracil at an initial dose of  $370 \text{ mg/m}^2$  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). For patients who experienced no toxicity in the prior treatment course, 5-fluorouracil dosage may be increased by 10%. Calcium Leucovorin dosages are not adjusted for toxicity.

## **4.3 Contraindications**

Calcium Leucovorin is improper therapy for pernicious anaemia and other megaloblastic anaemias secondary to the lack of Vitamin B<sub>12</sub>. When treating these conditions with Calcium Leucovorin, haematological remission may occur, but neurological manifestations are likely to progress.

Known hypersensitivity to calcium folinate or to any of the excipients.

#### **4.4 Special warnings and precautions for use**

**Injection:** Calcium 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.

Calcium Leucovorin 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. Simultaneous therapy with a folic acid antagonist and Calcium Leucovorin 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.

Because of the Ca<sup>2+</sup> content of the Calcium Leucovorin injections, no more than 16 mL of the 10 mg/mL formulations (160 mg of Calcium Leucovorin) should be injected intravenously per minute.

Calcium Leucovorin may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhoea and dehydration have been reported in elderly patients receiving Calcium Leucovorin 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 Calcium Leucovorin, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases. Since three patients had recurrent neurological symptoms on rechallenge with Calcium Leucovorin, further treatment with Calcium Leucovorin 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 Calcium Leucovorin.

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

Calcium Leucovorin 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, 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 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:**

Calcium Leucovorin 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 leucovorin 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 Calcium Leucovorin/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 Calcium Leucovorin/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.

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.

### **Laboratory Tests - Combination therapy with 5-Fluorouracil:**

Patients being treated with the Calcium Leucovorin /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:

<b>Diarrhoea and/or Stomatitis</b>	<b>WBC/mm<sup>3</sup> Nadir</b>	<b>Platelets/mm<sup>3</sup> Nadir</b>	<b>5-FU Dose</b>
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/mm<sup>3</sup>. 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.

### ***Calcium folinate/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 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 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 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.

### **Laboratory tests**

#### **5-FU/calcium folinate 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/calcium folinate 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  $\geq 7.0$ .

## **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 neutralized.

Folic acid in large amounts may counteract the antiepileptic effect of cotrimoxazole, phenobarbital, phenytoin and primidone, methotrexate 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 Adverse effects (undesirable effects)). High oral, intravenous or intramuscular doses of Calcium Leucovorin may reduce the efficacy of intrathecally administered methotrexate. Calcium Leucovorin may enhance the toxicity of fluorouracil (see section 4.4).

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 data available.

### 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. There are no indications that folic acid induces harmful effects if administered during pregnancy. 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.

### 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 Calcium Leucovorin is administered to a nursing mother.

## 4.7 Effects on ability to drive and use machines

Calcium Leucovorin 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 DL - Monotherapy	
System Organ Class	ADR Term
Immune system disorders	Hypersensitivity Anaphylactic reaction Anaphylactic shock
Nervous system disorders	Seizure Syncope
Skin and subcutaneous tissue disorders	Urticaria



General disorders and administration site conditions	Pyrexia
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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:

<b>Adverse Drug Reactions Leucovorin, Calcium DL - Combination Therapy</b>	
<b>System Organ Class</b>	<b>ADR Term</b>
Blood and lymphatic system disorders	Leukopenia Neutropenia Thrombocytopenia Anaemia
Metabolism and nutrition disorders	Hyperammonaemia
Gastrointestinal disorders	Nausea Vomiting Diarrhoea Stomatitis
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, Calcium Leucovorin 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

Peak plasma levels of folinic acid are reached, on average 40 minutes and 1.7 hours after intramuscular and oral administration, respectively. The bioavailability of an oral dose is almost the same as an equivalent intramuscular dose.

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.

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.

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

### 5.3 Preclinical safety data

#### Genotoxicity

No data available.

#### Carcinogenicity

No data available.

#### Reproductive and developmental toxicity

No data available.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Injection:* Sodium chloride, Water for Injections

*Tablet:* Lactose monohydrate, Microcrystalline cellulose, Magnesium stearate

### 6.2 Incompatibilities

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

### 6.3 Shelf life

*Injection:* 24 months.

*Tablets:* 36 months.

### 6.4 Special precautions for storage

*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

Strength	Dose Form	Pack size
15 mg	2 mL ampoule, glass	5
50 mg	5 mL vial, glass	1
300 mg	30 mL vial, glass	1
15 mg	Tablet	10

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

*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

Solution for injection 15 mg/2mL: 29 July 1982

Solution for injection 50 mg/5mL: 29 July 1982

Solution for injection 300 mg/30mL: 24 November 1998

Tablets 15 mg: 19 March 1987

## 10. DATE OF REVISION OF THE TEXT

11 February 2020

### Summary table of changes

Section changed	Summary of new information
4.2	Foods, drinks and drugs that may increase urinary acidity should be avoided during the therapy added.
4.3	“Known hypersensitivity to calcium folinate or to any of the excipients” added
4.4	More warnings and safety added.
4.5	More interactions added.
4.6	Pregnancy updated.
4.8	Adverse effects updated.
4.9	Overdose updated.
6.2	incompatibility with injectable forms of methotrexate, fluororacil, foscarenet added.