CALCIUM FOLINATE

Leucovorin Calcium

50 mg/5 mL Solution for Injection (IM/IV)

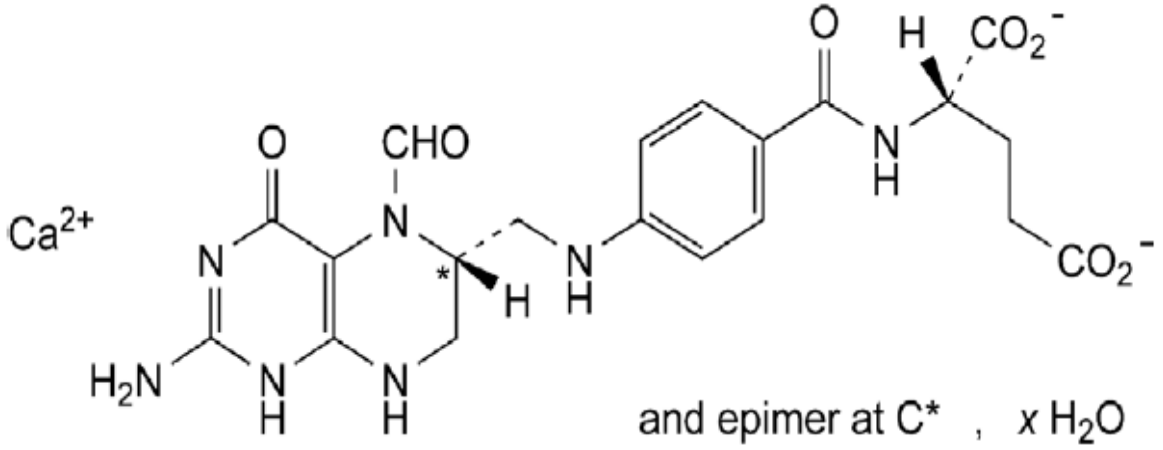
1.0 PHARMACOLOGIC CATEGORY

Detoxifying Agent for Antineoplastic Agent

2.0 DESCRIPTION

Calcium Folinate (Leucovorin Calcium) 50 mg/5 mL Solution for Injection (IM/IV) is a clear straw to pale yellow colored sterile, isotonic solution free from visible particulate matter. The solution does not contain a bactericide.

The chemical structure of calcium folinate is shown below, CAS registry number 2060570-47-8.



Chemical name: Calcium (2*S*)-2-[[4-[[[(6*RS*)-2-amino-5-formyl-4-oxo1,4,5,6,7,8-hexahydropteridin-6-yl] methyl] amino] benzoyl] amino] pentanedioate

Chemical Formula: $C_{20}H_{21}CaN_7O_7$, xH_2O

M.W. = 511.5 (Anhydrous)

3.0 FORMULATION/COMPOSITION

Each vial of Calcium Folinate (Leucovorin Calcium) contains 10 mg folinic acid per mL.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Folinic acid has shown good results in the treatment of certain megaloblastic anemias 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.

Folinic acid has also shown good results in reducing the toxicity and circumventing the effect

of folic acid antagonists, if therapeutically desired.

4.2 Dosage and Method of Administration

Dosage

Calcium Folinate (*Leucovorin Calcium****)*** *rescue after methotrexate therapy*

The recommendations for Calcium Folinate (Leucovorin Calcium) rescue are based on a methotrexate dose of 12 to 15 g/m^2 administered by intravenous infusion over four hours (see product information for methotrexate). Calcium Folinate (Leucovorin Calcium) rescue at a dose of 15 mg (approximately 10 mg/m^2) every six hours for ten doses starts 24 hours after the beginning of the methotrexate infusion.

In the presence of gastrointestinal toxicity, nausea or vomiting, Calcium Folinate (Leucovorin Calcium) should be administered parenterally. Serum creatinine and methotrexate levels should be determined at least once daily. Calcium Folinate (Leucovorin Calcium) Injection administration, hydration and urinary alkalinization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5 x 10^{-8} M (0.05 micromolar). Foods, drinks and drugs that may increase urinary acidity should be avoided during the therapy.

The Calcium Folinate (Leucovorin Calcium) dose should be adjusted or folinic acid rescue extended based on the following guidelines shown in Table 1.

Table 1: Guidelines for Calcium Folinate (Leucovorin Calcium) dosage and administration

Clinical situation/laboratory findings	Calcium Folinate (Leucovorin Calcium) dosage and duration
Normal methotrexate elimination Serum methotrexate level approximately 10 µM at 24 hours after administration, 1 µM at 48 hours, and less than 0.2 µM at 72 hours.	15 mg intramuscularly or intravenously every six hours for 60 hours (ten 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 intramuscularly or intravenously every six hours until methotrexate level is less than 0.05 µM.

Patients who experience delayed methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate Calcium Folinate (Leucovorin Calcium) therapy, these patients require continuing hydration and urinary alkalinization and close monitoring of fluid and electrolyte status until the serum methotrexate level has fallen to below 0.05 µM 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, Calcium Folinate (Leucovorin Calcium) 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.

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

Monitoring of serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with Calcium Folinate (Leucovorin Calcium). 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 Calcium Folinate (Leucovorin Calcium) or prolonged administration may be indicated.

Calcium Folinate (Leucovorin Calcium) rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion. Calcium Folinate (Leucovorin Calcium) 10 mg/m^2 should be administered intravenously, intramuscularly every six hours until the serum methotrexate level is less than 0.01 μM.

In the presence of gastrointestinal toxicity, nausea or vomiting, Calcium Folinate (Leucovorin Calcium) should be administered parenterally. Serum creatinine and methotrexate levels should be determined at intervals of 24 hours. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5 μM or the 48 hour level is greater than 0.9 μM, the dose of Calcium Folinate (Leucovorin Calcium) should be increased to 100 mg/m^2 intravenously every three hours until the methotrexate level is less than 0.01 μM.

Hydration (3 L/day) and urinary alkalinization with sodium bicarbonate solution should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Treatment of megaloblastic anemias
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 Calcium Folinate (Leucovorin Calcium) is not utilized 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 leukocyte counts have reached safe levels.

Method of administration
Folinic acid may be given parenterally by intramuscular injection, intravenous injection or intravenous infusion. Folinic acid should not be administered intrathecally.

Calcium Folinate (Leucovorin Calcium) Injection may be given parenterally by intramuscular injection, intravenous injection or intravenous infusion. Calcium Folinate (Leucovorin Calcium) Injection should NOT be administered intrathecally. When Calcium Folinate (Leucovorin Calcium) Injection has been administered intrathecally following intrathecal overdose of methotrexate, death has been reported (see **Section 4.4 Special Warnings and Precautions for Use**).

Because of the calcium ion content of the Calcium folinate injections, no more than 160 mg (16 mL of the 50 mg/5 mL or 300 mg/30 mL formulation) should be injected intravenously per minute.

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

When required for intravenous infusion, Calcium Folinate (Leucovorin Calcium) Injection may be diluted in 1 liter 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 discoloration prior to administration where solution and container permit. Do not use if solution is cloudy or precipitated.

Patient monitoring laboratory tests
Methotrexate/folinic acid therapy
Patients being treated with Calcium Folinate (Leucovorin Calcium) 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. In cases of methotrexate overdose or delayed excretion, monitor urine pH as appropriate, to ensure maintenance of pH $\geq$ 7.0.

Calcium Folinate (Leucovorin Calcium) dosage should be adjusted on the basis of laboratory test results.

5-Fluorouracil/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.

4.3 Contraindications

Calcium Folinate (Leucovorin Calcium) therapy is contraindicated in patients with:

- Pernicious anemia and other megaloblastic anemias secondary to the lack of Vitamin B12. When treating these conditions with folinic acid, hematological remission may occur, but neurological manifestations are likely to progress.

- Known hypersensitivity to the active substance(s) or to any of the excipients.

4.4 Special Warnings and Precautions for Use

Folinic acid should be administered only 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 (see **Section 4.2 Dosage and Method of Administration**).

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

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

Simultaneous therapy with a folic acid antagonist and folinic acid is not recommended because the effect of the folic acid antagonist is either reduced or completely inhibited (see **Section 4.5 Interactions with Other Medicinal Products and Other Forms of Interactions**).

Many cytotoxic medicinal products - direct or indirect DNA synthesis inhibitors - lead to macrocytosis (hydrocarbamide, cytarabine, mercaptopurine, thioguanine). Such macrocytosis should not be treated with folinic acid.

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 (see **Section 4.8 Undesirable Effects**, Nervous system disorders).

Since three patients had recurrent neurological symptoms on rechallenge with folinic acid, further treatment with folinic acid is not recommended in these circumstances.

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 **Section 4.5 Interactions with Other Medicinal Products and Other Forms of Interactions**).

Folinic acid/Methotrexate
An accidental overdose with a folate antagonist, such as methotrexate, should be treated

quickly as a medical emergency. As the time interval between methotrexate administration and folinic acid rescues increases, folinic acid effectiveness in counteracting toxicity decreases.

Folinic acid has no effect on non-hematological toxicities of methotrexate, such as nephrotoxicity resulting from drug 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 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 folinic acid.

Excessive folinic acid doses must be avoided since this might impair the antitumor activity of methotrexate, especially in CNS tumors where folinic acid accumulates after repeated courses.

Resistance to methotrexate as a result of decreased membrane transport implies resistance to folinic acid rescue as both medicinal products share the same transport system.

Folinic Acid/Fluorouracil
Folinic acid must not be mixed with fluorouracil in the same IV injection or infusion. Folinic acid may enhance the toxicity profile of fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis and/or diarrhea, which may be dose limiting. In addition, hematological adverse reactions have been observed. Deaths from severe enterocolitis, diarrhea and dehydration have been reported in elderly patients receiving fluorouracil and folinic acid. Concomitant granulocytopenia and fever were present in some but not all patients. When folinic acid and fluorouracil are used in combination, in cases of toxicity the fluorouracil dosage has to be reduced more than when fluorouracil is used alone.

Combined folinic acid/fluorouracil treatment should not be initiated or maintained in patients with symptoms of gastrointestinal (GI) toxicity, regardless of the severity, until all of these symptoms have completely disappeared.

Because diarrhea may be a sign of GI toxicity, patients presenting with diarrhea must be carefully monitored until the symptoms have disappeared completely, since rapid clinical deterioration leading to death can occur. If diarrhea and/or stomatitis occur, it is advisable to reduce the dose of fluorouracil until symptoms have fully disappeared. Especially the elderly and patients with a low physical performance due to their illness are prone to these toxicities.

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

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.

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

Use in the elderly
Elderly patients are at increased risk of severe toxicity when receiving combination therapy of folinic acid and fluorouracil. Particular care should be taken when treating these patients.

Pediatric use
There are no data available on use in children.

Effects on laboratory tests
No data available.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbitone, phenytoin, primidone and succinimides, and increase the frequency of seizures in susceptible children, and 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 **Sections 4.4 Special Warnings and Precautions for Use** and **4.8 Undesirable Effects**). 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.

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

Folinic acid may enhance the toxicity of fluorouracil. When folinic acid 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.

Concurrent administration of chloramphenicol and folic acid in folate deficient patients may result in antagonism of hematopoietic response to folic acid. Folinic acid may enhance the toxicity of fluorouracil (see **Sections 4.2 Dosage and Method of Administration, 4.4 Special Warnings and Precautions for Use** and **4.8 Undesirable Effects**).

4.6 Fertility, Pregnancy and Lactation

Effects on fertility
No data available.

Use in pregnancy - Category A
There are no adequate and well-controlled clinical studies conducted in pregnant or breastfeeding woman. No formal animal reproductive toxicity studies with folinic acid 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 folinic acid to diminish toxicity or counteract the effects.

Fluorouracil use is generally contraindicated during pregnancy and contraindicated during breastfeeding; this applies also to the combined use of folinic acid with fluorouracil.

Use in 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 folinic acid is administered to a breastfeeding mother.

4.7 Effects on Ability to Drive and Use Machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable Effects

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following parenteral administration of folinic acid. Nausea and vomiting with very high doses of folinic acid have been reported.

In addition, hematological adverse reactions, such as leukocytopenia, neutropenia, anemia and thrombocytopenia, may occur. These adverse reactions are dose dependent and their occurrence can usually be decreased by reducing the dosage of cytotoxic drugs. To control these adverse reactions, hematological values e.g. blood leukocyte and thrombocyte levels, and serum electrolyte (e.g. Na, K, Ca) and creatinine levels should be closely monitored.

Immune system disorders
Frequency undetermined: Hypersensitivity.
Very rare (< 0.1%): Anaphylactoid/anaphylactic reactions and anaphylactic shock.

Psychiatric disorders
Rare (0.01 - 0.1%): Insomnia, agitation and depression after high doses.

Nervous system disorders
Rare (0.01 - 0.1%): Increase in the frequency of attacks in epileptic patients (also see **Section 4.5 Interactions with Other Medicinal Products and Other Forms of Interaction),** seizures and/or syncope.

Skin and subcutaneous tissue disorders
Frequency undetermined: Urticaria.

Gastrointestinal disorders
Rare (0.01 - 0.1%): Gastrointestinal disorders after high doses: abdominal pain

General disorders and administrations site conditions
Uncommon (0.1 - 1%): Pyrexia after administration of folinic acid as solution for injection

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

Folinic Acid in combination with fluorouracil
Generally, the safety profile of folinic acid depends on the applied regimen of fluorouracil due to enhancement of fluorouracil-induced toxicities.

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**).

Additional undesirable effects of folinic acid when used in combination with fluorouracil are listed below:

Metabolis*m* and nutrition disorders
Frequency undetermined: Hyperammonemia.

Blood and lymphatic system disorders
Very common (> 10%): bone marrow failure, including fatal cases.

General disorders and administration site condition
Very common (> 10%): Mucositis. Fatalities have occurred as a result of mucositis.

Skin and subcutaneous tissue disorders
Common (1 - 10%): Palmar-Palmar Erythrodysesthesia syndrome (hand-foot syndrome).

Gastrointestinal disorders
Very common (> 10%): Nausea and vomiting, diarrhea, stomatitis, cheilitis.

The most common dose-limiting adverse reaction occurring in patients receiving combination of folinic acid and fluorouracil are stomatitis and diarrhea.

Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhea) and myelosuppression. In patients with diarrhea, rapid clinical deterioration leading to death can occur (see **Section 4.4 Special Warnings and Precautions for Use**).

4.9 Overdose and Treatment

Folinic acid is an intermediate in the metabolism of folinic 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 nullify the chemotherapeutic effect of folic acid antagonists.

In case of overdose, immediately seek medical help.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action
Folinic acid is the formyl derivative of tetrahydrofolic acid which is a metabolite and active form of folic acid. Folinic acid as a co-factor participates in many metabolic reactions including purine synthesis, pyrimidine synthesis and amino acid conversion. It is effective in the treatment of megaloblastic anemia caused by folic acid deficiency and is a potent antidote for both the hematopoietic and reticuloendothelial toxic effects of folic acid antagonists, e.g. methotrexate, pyrimethamine, trimethoprim.

Folinic acid is used in cytotoxic therapy as an antidote to folic acid antagonists which block conversion of folic acid to tetrahydrofolate by binding enzyme dihydrofolate reductase. In some cancers, folinic acid enters and 'rescues' normal cells, in preference to tumor 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

Absorption
Following administration, folinic acid enters the general body pool of reduced folates. It has been reported that, following intravenous, intramuscular administration, peak serum level of total reduced folates are achieved within a mean time of 10 minutes, 52 minutes and 1.7 hours, respectively. Peak levels of 5-formyl THF appear at 10 minutes and 28 minutes following intravenous and intramuscular administration respectively

Distribution
Folate is concentrated in the cerebrospinal fluid and liver although distribution occurs to all body tissues. The bioavailability of an oral dose is almost the same as an equivalent intramuscular dose.

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

Reduction in the levels of parent compound coincides with the appearance of the active metabolite 5- methyl THF, which becomes the major circulating form of the drug. Peak levels are observed at 1.5 and 2.8 hours following intravenous and intramuscular administration respectively. The terminal half-life for total reduced folates is reported as 6.2 hours. 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.

Excretion
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.

6.0 PHARMACEUTICAL PARTICULARS

6.1 Shelf-Life

24 Months

6.2 Storage Conditions

Store between 2°C - 8°C.

6.3 Availability

Calcium Folinate (Leucovorin Calcium) Injection vial 50 mg/5 mL is a clear, straw to pale yellow colored solution free from visible particulate matter containing 10 mg of folinic acid per mL. It is filled in a 5 mL Type I clear glass vial with a chlorobutyl rubber stopper - single vial per pack.

6.4 Incompatibilities

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

For more information refer to **Section 4.5 Interactions with Other Medicinal Products and Other Forms of Interactions**.

6.5 Special Precautions for Disposal and Other Handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.0 FDA REGISTRATION NUMBER

Calcium Folinate (Leucovorin Calcium) 50 mg/5 mL Solution for Injection (IM/IV):DR-XY23624

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Calcium Folinate (Leucovorin Calcium) 50 mg/5 mL Solution for Injection (IM/IV): 09 June

2014

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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