

LEUCOVORIN CALCIUM- leucovorin calcium tablet

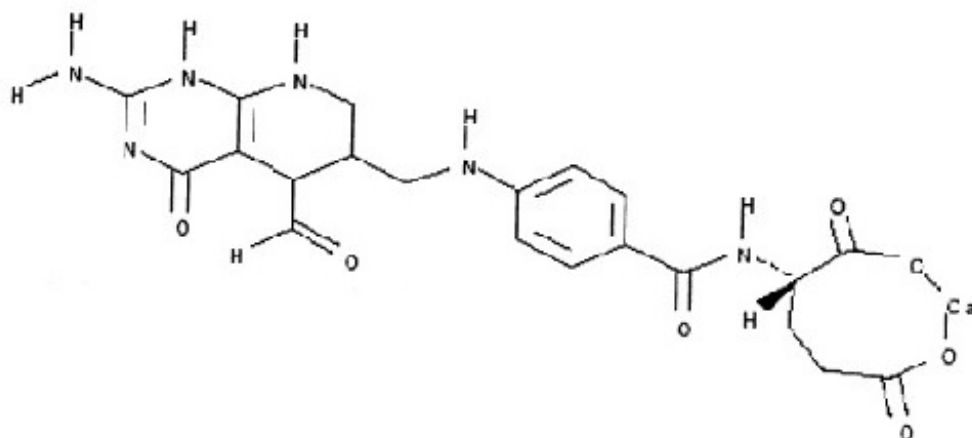
Epic Pharma LLC

Leucovorin Calcium Tablets, USP 5 mg, 10 mg, 15 mg and 25 mg Rx only

DESCRIPTION

Leucovorin calcium tablets USP contain either 5 mg, 10 mg, 15 mg or 25 mg leucovorin as the calcium salt of *N*-[4-[[[(2-amino-5-formyl-1,4,5,6,7,8-hexahydro-4-oxo-6-pteridiny)methyl]amino]benzoyl]-*L*-glutamic acid. This is equivalent to either 5.4 mg, 10.8 mg, 16.21 mg or 27.01 mg of anhydrous leucovorin calcium, respectively. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose anhydrous, magnesium stearate, and microcrystalline cellulose.

Leucovorin is a water-soluble form of reduced folate in the folate group; it is useful as an antidote to drugs which act as folic acid antagonists. These tablets are intended for oral administration only. The structural formula of leucovorin calcium is:



$C_{20}H_{21}CaN_7O_7$ MW 511.51

CLINICAL PHARMACOLOGY

Leucovorin is a racemic mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid. The biologically active compound of the mixture is the (-)-*L*-isomer, known as *Citrovorum factor*, or (-)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of "one-carbon" moieties. Following oral administration, leucovorin is rapidly absorbed and enters the general body pool of reduced folates. The increase in plasma and serum folate activity (determined microbiologically with *Lactobacillus casei*) seen after oral administration of leucovorin is predominantly due to 5-methyltetrahydrofolate.

Twenty normal men were given a single, oral 15 mg dose (7.5 mg/m²) of leucovorin calcium and serum folate concentrations were assayed with *L. casei*. Mean values

observed (\pm one standard error) were:

- a) Time to peak serum folate concentration: 1.72 ± 0.08 hours,
- b) Peak serum folate concentration achieved: 268 ± 18 ng/mL,
- c) Serum folate half-disappearance time: 3.5 hours.

Oral tablets yielded areas under serum folate concentration-time curves (AUCs) that were 12% greater than equal amounts of leucovorin given intramuscularly and equal to the same amounts given intravenously.

Oral absorption of leucovorin is saturable at doses above 25 mg. The apparent bioavailability of leucovorin was 97% for 25 mg, 75% for 50 mg and 37% for 100 mg.

INDICATIONS AND USAGE

Leucovorin calcium tablets are indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosages of folic acid antagonists.

CONTRAINDICATIONS

Leucovorin is improper therapy for pernicious anemia and other megaloblastic anemias secondary to the lack of Vitamin B₁₂. A hematologic remission may occur while neurologic manifestations continue to progress.

WARNINGS

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

Monitoring of the serum methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin.

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

Leucovorin may enhance the toxicity of fluorouracil. Deaths from severe enterocolitis, diarrhea, and dehydration have been reported in elderly patients receiving weekly leucovorin and fluorouracil.¹ Concomitant granulocytopenia and fever were present in some but not all of the patients.

The concomitant use of leucovorin with trimethoprim-sulfamethoxazole for the acute treatment of *Pneumocystis carinii* pneumonia in patients with HIV infection was associated with increased rates of treatment failure and mortality in a placebo-controlled study.

PRECAUTIONS

General

Parenteral administration is preferable to oral dosing if there is a possibility that the patient may vomit or not absorb the leucovorin. Leucovorin has no effect on other established toxicities of methotrexate such as the nephrotoxicity resulting from drug and/or metabolite precipitation in the kidney.

Drug Interactions

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

Preliminary animal and human studies have shown that small quantities of systemically administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1 to 3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration. However, high doses of leucovorin may reduce the efficacy of intrathecally administered methotrexate.

Leucovorin may enhance the toxicity of fluorouracil (see **WARNINGS**).

Pregnancy

Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with leucovorin. It is also not known whether leucovorin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Leucovorin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

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 leucovorin is administered to a nursing mother.

Pediatric Use

See **Drug Interactions** subsection.

ADVERSE REACTIONS

Allergic sensitization, including anaphylactoid reactions and urticaria, has been reported following the administration of both oral and parenteral leucovorin.

OVERDOSAGE

Excessive amounts of leucovorin may nullify the chemotherapeutic effect of folic acid antagonists.

DOSAGE AND ADMINISTRATION

Leucovorin calcium tablets are intended for oral administration. Because absorption is

saturable, oral administration of doses greater than 25 mg is not recommended.

Impaired Methotrexate Elimination or Inadvertent Overdosage: Leucovorin rescue should begin as soon as possible after an inadvertent overdosage and within 24 hours of methotrexate administration when there is delayed excretion (see **WARNINGS**)². Leucovorin 15 mg (10 mg/m²) should be administered IM, IV, or PO every 6 hours until serum methotrexate level is less than 10⁻⁸M. In the presence of gastrointestinal toxicity, nausea or vomiting, leucovorin should be administered parenterally.

Serum creatinine and methotrexate levels should be determined at 24-hour intervals. If the 24 hour serum creatinine has increased 50% over baseline or if the 24 hour methotrexate level is greater than 5 x 10⁻⁶M or the 48 hour level is greater than 9 x 10⁻⁷M, the dose of leucovorin should be increased to 150 mg (100 mg/m²) IV every 3 hours until the methotrexate level is less than 10⁻⁸M. Doses greater than 25 mg should be given parenterally (see).

Hydration (3 L/d) and urinary alkalinization with sodium bicarbonate should be employed concomitantly. The bicarbonate dose should be adjusted to maintain the urine pH at 7 or greater.

The recommended dose of leucovorin to counteract hematologic toxicity from folic acid antagonists with less affinity for mammalian dihydrofolate reductase than methotrexate (i.e., trimethoprim, pyrimethamine) is substantially less, and 5 to 15 mg of leucovorin per day has been recommended by some investigators.

Patients who experience delayed early methotrexate elimination are likely to develop reversible non-oliguric renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalinization, and close monitoring of fluid and electrolyte status, until serum methotrexate level has fallen 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. These abnormalities may or may not be associated with significant clinical toxicity. If significant clinical toxicity is observed, 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 reconsidered when laboratory abnormalities or clinical toxicities are observed.

HOW SUPPLIED

Leucovorin Calcium Tablets USP, 5 mg are off-white, round biconvex tablets, debossed "€" above "**358**" on one side and bisected on the other side and are supplied as follows.

NDC 42806-358-30 Bottles of 30

NDC 42806-358-01 Bottles of 100

Leucovorin Calcium Tablets USP, 10 mg are off-white, round biconvex tablets, debossed "€" above "**133**" on one side and bisected on the other side and are supplied as follows.

NDC 42806-133-21 Bottles of 12

NDC 42806-133-24 Bottles of 24

Leucovorin Calcium Tablets USP, 15 mg are off-white, round biconvex tablets, debossed "€" above "**134**" on one side and bisected on the other side and are supplied as follows.

NDC 42806-134-24 Bottles of 24

Leucovorin Calcium Tablets USP, 25 mg are off-white, round biconvex tablets, debossed "€" above "**359**" on one side and bisected on one side and plain on the other side and are supplied as follows.

NDC 42806-359-25 Bottles of 25

Store at Controlled Room Temperature 15° to 30°C (59° to 86°F). **Protect from light and moisture.**

REFERENCES

1. Grem JL, Shoemaker DD, Petrelli NJ, Douglas HO. Severe and fatal toxic effects observed in treatment with high- and low-dose leucovorin plus 5-fluorouracil for colorectal carcinoma. Cancer Treat Rep 1987; 71: 1122.
2. Link MP, Goorin AM, Miser AW et al. The effect of adjuvant chemotherapy on relapse-free survival patients with osteosarcoma of the extremity. N Engl J Med 1986; 314:1600 - 1606.

Distributed by:

Epic Pharma, LLC

Laurelton, NY 11413

Rev. 06-2023-00



MF358REV06/23

OE2930



PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - Leucovorin Calcium Tablets USP, 5 mg 100ct

No Varnish	*Each Tablet Contains: Leucovorin calcium, USP equivalent to 5 mg leucovorin.	NDC 42806-358-01	Protect from light and moisture.	 3 42806-358-01 6
	USUAL DOSAGE: See package insert for complete prescribing information. Dispense in a tight, light-resistant container as defined in the USP. LE4195 Rev. 08-2019-00	Leucovorin Calcium Tablets, USP 5 mg* Rx Only 100 Tablets	Store at Controlled Room Temperature 15° to 30°C (59° to 86°F). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.	
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PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - Leucovorin Calcium Tablets USP, 10 mg 12ct

No Varnish	*Each Tablet Contains: Leucovorin calcium, USP equivalent to 10 mg leucovorin.	NDC 42806-133-21	Protect from light and moisture.	 N 3 42806-133-21 7
	USUAL DOSAGE: See package insert for complete prescribing information. Dispense in a tight, light-resistant container as defined in the USP.	Leucovorin Calcium Tablets, USP 10 mg*	Store at Controlled Room Temperature 15° to 30°C (59° to 86°F). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.	
	LE4210 Rev. 10-2019-00	Rx Only 12 Tablets		
	Distributed by: Epic Pharma, LLC Laurelton, NY 11413			

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - Leucovorin Calcium Tablets USP, 15 mg 24ct

No Varnish	*Each Tablet Contains: Leucovorin calcium, USP equivalent to 15 mg leucovorin.	NDC 42806-134-24	Protect from light and moisture.	 N 3 42806-134-24 5
	USUAL DOSAGE: See package insert for complete prescribing information. Dispense in a tight, light-resistant container as defined in the USP.	Leucovorin Calcium Tablets, USP 15 mg*	Store at Controlled Room Temperature 15° to 30°C (59° to 86°F). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.	
	LE4220 Rev. 10-2019-00	Rx Only 24 Tablets		
	Distributed by: Epic Pharma, LLC Laurelton, NY 11413			

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL - Leucovorin Calcium Tablets USP, 25 mg 25ct

No Varnish	*Each Tablet Contains: Leucovorin calcium, USP equivalent to 25 mg leucovorin.	NDC 42806-359-25	Protect from light and moisture.	 N 3 42806-359-25 9
	USUAL DOSAGE: See package insert for complete prescribing information. Dispense in a tight, light-resistant container as defined in the USP.	Leucovorin Calcium Tablets, USP 25 mg*	Store at Controlled Room Temperature 15° to 30°C (59° to 86°F). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.	
	LE4200 Rev. 08-2019-00	Rx Only 25 Tablets		
	Distributed by: Epic Pharma, LLC Laurelton, NY 11413			

LEUCOVORIN CALCIUM

leucovorin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:42806-358
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
LEUCOVORIN CALCIUM (UNII: RPR1R4C0P4) (LEUCOVORIN - UNII:Q573I9DVLP)	LEUCOVORIN	5 mg

Inactive Ingredients	
Ingredient Name	Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM PALMITOSTEARATE (UNII: R4OXA9G5BV)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	

Product Characteristics			
Color	WHITE (off-white)	Score	2 pieces
Shape	ROUND	Size	8mm
Flavor		Imprint Code	E;358
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42806-358-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2020	
2	NDC:42806-358-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2020	

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA074544	04/16/2020	

LEUCOVORIN CALCIUM

leucovorin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:42806-133

Route of Administration		ORAL		
Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
LEUCOVORIN CALCIUM (UNII: RPR1R4C0P4) (LEUCOVORIN - UNII:Q573I9DVLP)		LEUCOVORIN	10 mg	
Inactive Ingredients				
Ingredient Name			Strength	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)				
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)				
MAGNESIUM PALMITOSTEARATE (UNII: R4OXA9G5BV)				
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
Product Characteristics				
Color	WHITE (off-white)	Score	2 pieces	
Shape	ROUND	Size	8mm	
Flavor		Imprint Code	E;133	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42806-133-21	12 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2021	
2	NDC:42806-133-24	24 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2021	
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
ANDA	ANDA074544		01/01/2021	

LEUCOVORIN CALCIUM

leucovorin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:42806-134
Route of Administration	ORAL		

Active Ingredient/Active Moiety				
Ingredient Name		Basis of Strength	Strength	
LEUCOVORIN CALCIUM (UNII: RPR1R4C0P4) (LEUCOVORIN - UNII:Q573I9DVLP)		LEUCOVORIN	15 mg	
Inactive Ingredients				
Ingredient Name			Strength	
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)				
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)				
MAGNESIUM PALMITOSTEARATE (UNII: R4OXA9G5BV)				
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
Product Characteristics				
Color	WHITE (off-white)	Score	2 pieces	
Shape	ROUND	Size	8mm	
Flavor		Imprint Code	E;134	
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42806-134-24	24 in 1 BOTTLE; Type 0: Not a Combination Product	01/01/2021	
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
ANDA	ANDA074544		01/01/2021	

LEUCOVORIN CALCIUM

leucovorin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:42806-359
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
LEUCOVORIN CALCIUM (UNII: RPR1R4C0P4) (LEUCOVORIN - UNII:Q573I9DVLP)		LEUCOVORIN	25 mg

Inactive Ingredients				
Ingredient Name				Strength
ANHYDROUS LACTOSE (UNII: 3SY5LH9PMK)				
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)				
MAGNESIUM PALMITOSTEARATE (UNII: R4OXA9G5BV)				
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)				
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)				
Product Characteristics				
Color	WHITE (off-white)		Score	2 pieces
Shape	ROUND		Size	8mm
Flavor			Imprint Code	E;359
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:42806-359-25	25 in 1 BOTTLE; Type 0: Not a Combination Product	04/16/2020	
Marketing Information				
Marketing Category	Application Number or Monograph Citation		Marketing Start Date	Marketing End Date
ANDA	ANDA074544		04/16/2020	

Labeler - Epic Pharma LLC (827915443)

Registrant - Epic Pharma LLC (827915443)

Establishment

Name	Address	ID/FEI	Business Operations
Epic Pharma LLC		827915443	MANUFACTURE(42806-358, 42806-133, 42806-134, 42806-359)

Revised: 11/2023

Epic Pharma LLC