LEUCOVORIN CALCIUM- leucovorin calcium tablet
West-Ward Pharmaceuticals Corp.

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

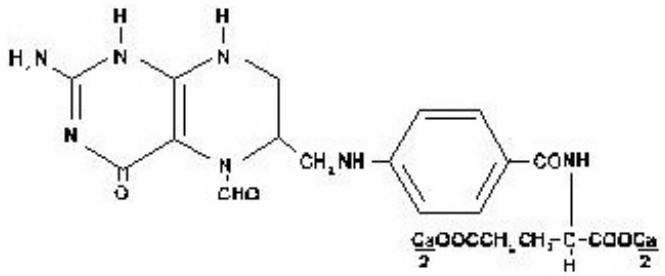
Rx only

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-pteridinyl)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 USP, respectively. In addition, each tablet contains the following *inactive ingredients*: colloidal silicon dioxide, croscarmellose sodium, D&C yellow #10 (15 mg and 25 mg), magnesium stearate, microcrystalline cellulose, povidone and pregelatinized starch.

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:



$C_{20}H_{21}CaN_7O_7$ M.W. 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/m^2) of leucovorin calcium and serum folate concentrations were assayed with *L. casei*. Mean values observed (± 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 the 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 is 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 B_{12}. A hematologic remission may occur while neurologic manifestations continue to progress.

WARNINGS

In the treatment of accidental overdosage 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). Leucovorin 15 mg (10 mg/m^2) should be administered IM, IV, or PO every 6 hours until the serum methotrexate level is less than 10^{-8} M. 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^{-6} M or the 48-hour level is greater than 9 x 10^{-7} M, the dose of leucovorin should be increased to 150 mg (100 mg/m^2) IV every 3 hours until the methotrexate level is less than 10^{-8} M. Doses greater than 25 mg should be given parenterally (see CLINICAL PHARMACOLOGY).

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 7.0 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 the 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 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/Storage and Handling

Leucovorin Calcium Tablets USP

5 mg tablets are supplied as an off-white, round, slightly biconvex tablet; scored on one side and product identification “54 293” debossed on the other side.

NDC 0054-8496-19: 5x10 Unit-Dose

NDC 0054-4496-13: Bottle of 30 Tablets

NDC 0054-4496-25: Bottle of 100 Tablets

10 mg tablets are supplied as an off-white, round, slightly biconvex tablet; scored on one side and product identification “54 942” debossed on the other side.

NDC 0054-4497-05: Bottle of 12 Tablets

NDC 0054-4497-10: Bottle of 24 Tablets

15 mg tablets are supplied as an yellow, round, slightly biconvex tablet; scored on one side and product identification “54 650” debossed on the other side.

NDC 0054-4498-10: Bottle of 24 Tablets

25 mg tablets are supplied as an yellow, round, slightly biconvex tablet; scored on one side and product identification “54 013” debossed on the other side.

NDC 0054-4499-11: Bottle of 25 Tablets

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

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 in patients with osteosarcoma of the extremity. *N Engl J Med* 1986;314:1600-1606.

Distr. by: **West-Ward**
Pharmaceuticals Corp.
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Revised October 2020

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

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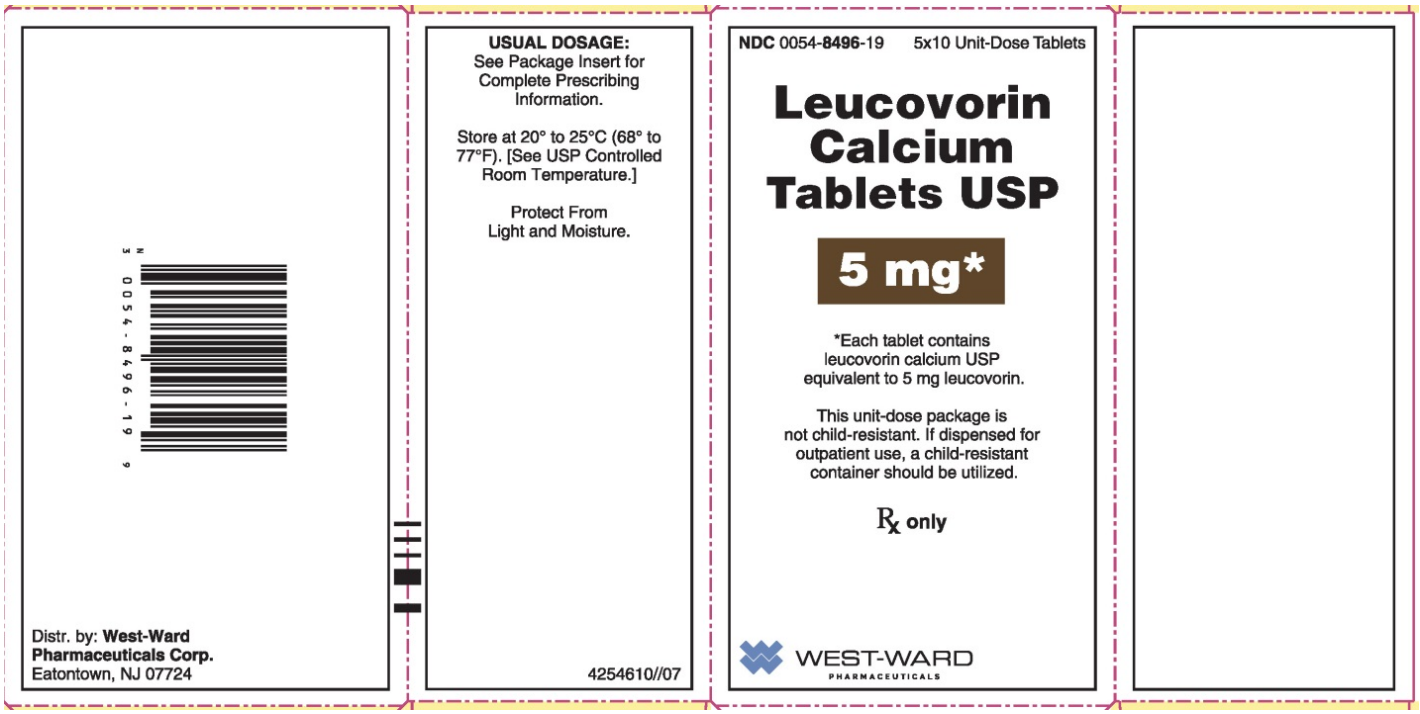

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

LEUCOVORIN CALCIUM

leucovorin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0054-4496
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**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	54;293
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0054-4496-25	100 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/1993	
2	NDC:0054-4496-13	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/1993	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072733	02/22/1993	

LEUCOVORIN CALCIUM

leucovorin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0054-4497
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**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	54;942
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0054-4497-10	24 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/1993	
2	NDC:0054-4497-05	12 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/1993	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072734	02/22/1993	

LEUCOVORIN CALCIUM

leucovorin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0054-4498
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**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics			
Color	YELLOW	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	54;650
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0054-4498-10	24 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/1993	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072735	02/22/1993	

LEUCOVORIN CALCIUM

leucovorin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0054-4499
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**
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	

D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics			
Color	YELLOW	**Score**	2 pieces
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	54;013
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-4499-11	25 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/1993	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072736	02/22/1993	

LEUCOVORIN CALCIUM

leucovorin calcium tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0054-8496
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
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
STARCH, CORN (UNII: O8232NY3SJ)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POVIDONE, UNSPECIFIED (UNII: FZ989GH94E)	

Product Characteristics			
Color	WHITE	**Score**	2 pieces
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	54;293
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0054-8496-19	5 in 1 CARTON	02/22/1993	
1		10 in 1 BLISTER PACK; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072733	02/22/1993	

Labeler - West-Ward Pharmaceuticals Corp. (080189610)

Establishment

Name	Address	ID/FEI	Business Operations
West-Ward Columbus Inc.		058839929	MANUFACTURE(0054-4496, 0054-4497, 0054-4498, 0054-4499, 0054-8496)

Revised: 10/2020 West-Ward Pharmaceuticals Corp.