LEUCOVORIN (Systemic)

Introduction

VA CLASSIFICATION (Primary/Secondary)¾VT102/AD900; BL400; AN400
Commonly used brand name(s):Wellcovorin.
Other commonly used names are citrovorum factor and folinic acid .

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Antidote (to folic acid antagonists); antianemic; antineoplastic adjunct.

Indications

Accepted

Methotrexate toxicity (prophylaxis and treatment)

Pyrimethamine toxicity (prophylaxis and treatment) or

Trimethoprim toxicity (prophylaxis and treatment)¾Leucovorin is indicated as an antidote to the toxic effects of folic acid antagonists such as methotrexate, pyrimethamine, or trimethoprim. Leucovorin also is indicated as a rescue after high-dose methotrexate therapy in osteosarcoma and as a part of chemotherapeutic treatment programs in the management of several forms of cancer.

Anemia, megaloblastic (treatment)¾Leucovorin is indicated to treat megaloblastic anemias associated with sprue, nutritional deficiency, pregnancy, and infancy when oral folic acid therapy is not feasible.
Leucovorin is not recommended for use in the treatment of pernicious anemia or other megaloblastic anemias secondary to lack of vitamin B 12, since it may produce a hematologic remission while neurologic manifestations continue to progress.

Carcinoma, colorectal (treatment adjunct)¾Leucovorin is indicated for use in combination with fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer 1.

[Carcinoma, head and neck (treatment adjunct)] *¾Leucovorin is indicated for use in combination with agents such as fluorouracil or high-dose methotrexate, as second-line treatment of squamous cell head and neck carcinoma. 8

[Ewing's sarcoma (treatment adjunct) or] *

[Lymphomas, non-Hodgkin's (treatment adjunct)] *¾Leucovorin is indicated for use in combination with high-dose methotrexate as second-line treatment of Ewing's sarcoma and non-Hodgkin's lymphomas. 8

[Tumors, trophoblastic (treatment adjunct)] *¾Leucovorin is indicated for use in combination with high-dose methotrexate as first-line treatment of gestational trophoblastic neoplasms. 8

Unaccepted

Leucovorin has not shown benefit over other regimens in the treatment of breast carcinomas. 8

Leucovorin has not shown benefit in the treatment of gastric carcinomas. 8

* Not included in Canadian product labeling.

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾511.51 7

Mechanism of action/Effect:

Antidote (to folic acid antagonists)¾Leucovorin is a reduced form of folic acid, which is readily converted to other reduced folic acid derivatives (e.g., tetrahydrofolate). Because it does not require reduction by dihydrofolate reductase as does folic acid, leucovorin is not affected by blockage of this enzyme by folic acid antagonists (dihydrofolate reductase inhibitors). This allows purine and thymidine synthesis, and thus DNA, RNA, and protein synthesis, to occur. Leucovorin may limit methotrexate action on normal cells by competing with methotrexate for the same transport processes into the cell. Leucovorin given at the appropriate time rescues bone marrow and gastrointestinal cells from methotrexate but has no apparent effect on pre-existing methotrexate nephrotoxicity.

Absorption:

Rapidly absorbed after oral administration; saturation of absorption is reached at doses greater than 25 mg. Bioavailability is approximately 97% for a 25-mg dose, 75% for a 50-mg dose, and 37% for a 100-mg dose 1, 2.

Distribution:

Crosses blood-brain barrier in moderate amounts; largely concentrated in liver.

Biotransformation:

Hepatic and intestinal mucosal, mainly to 5-methyltetrahydrofolate (active). After oral administration, leucovorin is substantially (greater than 90%) and rapidly (within 30 minutes) metabolized. Metabolism is less extensive (about 66% 6 after intravenous and 72% after intramuscular administration) and slower with parenteral administration.

Half-life:

Terminal half-life for total reduced folates¾6.2 hours 1.

Onset of action:

Oral¾20 to 30 minutes.
Intramuscular¾10 to 20 minutes.
Intravenous¾Less than 5 minutes.

Time to peak serum reduced folate concentration

Oral¾1.72 ± 0.8 hours.
Intramuscular¾0.71 ± 0.09 hour.

Peak serum reduced folate concentration

After 15 mg dose¾
Oral: 268 ± 18 nanograms per mL (approximately 1 micromolar [1 ´ 10 -6 Molar]).
Intramuscular: 241 ± 17 nanograms per mL (approximately 1 micromolar [1 ´ 10 -6 Molar]).

Duration of action:

All routes¾3 to 6 hours.

Elimination:

Renal¾80 to 90%.
Fecal¾5 to 8%.

Precautions to Consider

Pregnancy/Reproduction

Pregnancy¾Studies have not been done in either animals or humans.
FDA Pregnancy Category C.
Recommended for treatment of megaloblastic anemia caused by pregnancy.

Breast-feeding

It is not known whether leucovorin is distributed into breast milk. However, problems in humans have not been documented.

Pediatrics

Leucovorin may increase the frequency of seizures in susceptible pediatric patients by counteracting the anticonvulsant effects of barbiturates, hydantoin anticonvulsants, and primidone 1.

Geriatrics

No information is available on the relationship of age to the effects of leucovorin in geriatric patients. However, elderly patients are more likely to have age-related renal function impairment, which may require adjustment of dosage in patients receiving leucovorin as a rescue from the effects of high-dose methotrexate.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
Anticonvulsants, barbiturate or

Anticonvulsants, hydantoin or

Primidone

(large doses of leucovorin may counteract the anticonvulsant effects of these medications)

Fluorouracil

(concurrent use of leucovorin may increase the therapeutic and toxic effects of fluorouracil 1, 3 ; although the two medications may be used together for therapeutic advantage, caution is necessary 1)

Sulfamethoxazole and trimethoprim

(concurrent use of leucovorin may be associated with increased morbidity rates and treatment failure when used for the treatment of pneumonia due to Pneumocystis carinii in patients with human immunodeficiency virus (HIV) infection 1)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

For treatment of anemia (as the sole agent)

>> Pernicious anemia or

>> Vitamin B 12 deficiency

(may produce a partial hematologic response 6 while neurologic manifestations continue to progress)

This medication should be used with caution when the following medical problems exist

Sensitivity to leucovorin

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
For patients receiving high-dose methotrexate

>> Creatinine clearance determinations

(recommended prior to initiation of high-dose methotrexate with leucovorin rescue therapy or if serum creatinine concentrations increase by 50% or more)

>> Creatinine concentrations, serum

(recommended prior to and every 24 hours after each methotrexate dose, until plasma or serum methotrexate concentrations are less than 5 ´ 10 -8 Molar, to detect developing renal function impairment and predict methotrexate toxicity. An increase of greater than 50% over the pretreatment concentration at 24 hours is associated with severe renal toxicity)

>> Methotrexate concentrations, plasma or serum

(recommended by some clinicians every 12 to 24 hours after high-dose methotrexate administration to determine dose and duration of leucovorin treatment needed to maintain rescue. May aid in identifying patients with delayed methotrexate clearance; toxicity appears to be related at least as much to the length of time that methotrexate concentrations are elevated as to the peak concentrations achieved. In general, monitoring should continue until concentrations are less than 5 ´ 10 -8 Molar)

>> pH determinations, urine

(recommended prior to each dose of high-dose methotrexate therapy and about every 6 hours throughout leucovorin rescue, until plasma or serum methotrexate concentrations are less than 5 ´ 10 -8 Molar, to ensure that pH remains greater than 7 so as to minimize the risk of methotrexate nephropathy from precipitation of methotrexate or metabolites in urine)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence rare

Allergic reaction (skin rash, hives, or itching; wheezing); seizures¾reported with use in cancer chemotherapy 4

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Leucovorin (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Sensitivity to leucovorin
Use in children¾May increase frequency of seizures in susceptible pediatric patients
Other medical problems, especially pernicious anemia or vitamin B 12 deficiency (for treatment of anemia as the sole agent)
Proper use of this medication

>> Importance of taking as directed and not missing doses; taking at evenly spaced times

>> Checking with physician before discontinuing medication or if vomiting occurs shortly after dose is taken

>> Proper dosing
Missed dose: Checking with physician right away; possible need for additional leucovorin; importance of not increasing dose unless directed by physician
>> Proper storage
Side/adverse effects

Signs of potential side effects, especially allergic reaction and seizures

General Dosing Information

A 15-mg dose produces a serum reduced folate concentration of approximately 1 micromolar (1 ´ 10 -6 Molar).
For use as an antidote to folic acid antagonists

Patients receiving leucovorin as a "rescue" from the toxic effects of methotrexate should be under supervision of a physician experienced in high-dose methotrexate therapy.
Leucovorin should be administered orally or parenterally. Leucovorin should not be administered intrathecally for the treatment of accidental overdoses of intrathecally administered folic acid antagonists. Leucovorin may be harmful or fatal if administered intrathecally. 1
Parenteral administration of leucovorin is recommended if it appears that absorption may be impaired as a result of nausea and vomiting.
High-dose methotrexate administration should not be initiated unless leucovorin is physically present and ready to be administered 6 , since rescue is critical.

A variety of dosage schedules of leucovorin in combination with high-dose methotrexate have been used. Since this regimen is still largely investigational, the prescriber should consult the medical literature in choosing a specific dosage. Alkalinization of urine (with bicarbonate and/or acetazolamide) and intravenous hydration (1000 mL per square meter of body surface area over six hours prior to beginning the methotrexate infusion and 3000 mL per square meter of body surface area per day during the methotrexate infusion and for two days after the infusion is completed) are also important to prevent renal toxicity caused by methotrexate and/or its metabolites.
Administration of leucovorin should be consecutive to rather than simultaneous with methotrexate administration so as not to interfere with methotrexate's antineoplastic effects. However, leucovorin has been administered simultaneously with pyrimethamine and trimethoprim in oral or intramuscular doses ranging from 400 mcg (0.4 mg) to 5 mg to prevent megaloblastic anemia due to high doses of these medications.
In general, it is recommended that the first dose of leucovorin be administered within the first 24 to 42 hours of starting a high-dose methotrexate infusion (within 1 hour of an overdose), in a dosage to produce blood concentrations equal to or greater than methotrexate blood concentrations (leucovorin in a dose of 15 mg produces peak plasma concentrations of approximately 1 micromolar [1 ´ 10 -6 Molar]). Duration of leucovorin administration varies with the dosage of methotrexate and plasma concentrations achieved (including rate of elimination); in general, leucovorin administration is continued until methotrexate concentrations fall to less than 5 ´ 10 -8 Molar.
A larger dose and/or longer duration of leucovorin treatment may be required in patients with aciduria, ascites, dehydration, gastrointestinal obstruction, renal function impairment, or pleural or peritoneal effusions because excretion of methotrexate is slowed and the length of time for plasma methotrexate concentrations to decrease to nontoxic levels (<5 ´ 10 -8 Molar) is increased. It is recommended that duration of leucovorin administration in these patients be based on determination of plasma methotrexate concentrations.
For use as an adjunct to fluorouracil for colorectal carcinoma

Patients receiving leucovorin in combination with fluorouracil should be under supervision of a physician experienced in cancer chemotherapy 1.

Oral Dosage Forms

Note: The dosing and strengths of the dosage forms available are expressed in terms of leucovorin base (not the calcium salt).

LEUCOVORIN CALCIUM TABLETS USP

Usual adult and adolescent dose

Antidote (to folic acid antagonists)¾
To methotrexate¾
Oral, 10 mg (base) per square meter of body surface area every six hours until methotrexate blood concentrations fall to less than 5 ´ 10 -8 M. 2

To pyrimethamine or trimethoprim¾
Prevention¾Oral, 400 mcg (0.4 mg) to 5 mg (base) with each dose of the folic acid antagonist.
Treatment¾Oral, 5 to 15 mg (base) per day.
Megaloblastic anemia, secondary to folate deficiency¾

Oral, up to 1 mg (base) per day.

Note: Doses higher than 25 mg should be given parenterally because oral absorption is saturable at doses above 25 mg 2.

Usual pediatric dose

See Usual adult and adolescent dose.

Strength(s) usually available

U.S.¾5 mg (base) (Rx)[Wellcovorin (scored)] [Generic] (scored)

15 mg (base) (Rx) [Generic] (scored)

25 mg (base) (Rx)[Wellcovorin (scored)]

Canada¾5 mg (base) (Rx) [Generic] (scored)

15 mg (base) (Rx) [Generic] (scored)

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container. Protect from light 2.

Parenteral Dosage Forms

Note: The dosing and strengths of the dosage forms available are expressed in terms of leucovorin base (not the calcium salt).

LEUCOVORIN CALCIUM INJECTION USP

Usual adult and adolescent dose

Antidote (to folic acid antagonists)¾
To methotrexate (inadvertent overdose)¾
Intramuscular or intravenous, 10 mg (base) per square meter of body surface area every six hours until methotrexate blood concentrations fall to less than 5 ´ 10 -8 Molar.
Note:
If, at 24 hours following methotrexate administration, the serum creatinine is increased by 50% or greater over baseline or serum methotrexate is greater than 5 ´ 10 -6 Molar, the dose of leucovorin should be 100 mg (base) per square meter of body surface area every three hours intravenously until methotrexate concentrations are reduced to appropriate levels.

To pyrimethamine or trimethoprim¾
Prevention¾Intramuscular, 400 mcg (0.4 mg) to 5 mg (base) with each dose of the folic acid antagonist.

Treatment¾Intramuscular, 5 to 15 mg (base) per day.
Megaloblastic anemia, secondary to folate deficiency¾
Intramuscular, up to 1 mg (base) per day.

Note: Because of its calcium content, leucovorin calcium injection should be administered by intravenous injection slowly, at a rate that does not exceed 160 mg of leucovorin per minute. 5

Usual pediatric dose

See Usual adult and adolescent dose.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾10 mg (base) per mL (Rx) [Generic] (without preservative)

Packaging and storage:

Store in the refrigerator between 2 and 8 °C (36 and 46 °F). Protect from light. 5

Stability:

Intravenous solutions containing leucovorin calcium in lactated Ringer's injection, Ringer's injection, or 0.9% sodium chloride injection are stable for up to 24 hours at room temperature. When diluted in 5% dextrose in water injection or 10% dextrose injection, intravenous solutions containing leucovorin calcium are stable for 12 hours at room temperature. When diluted in 10% dextrose in 0.9% sodium chloride injection, solutions are stable for 6 hours at room temperature 5.

Incompatibilities:

Leucovorin calcium injection is incompatible with fluorouracil; precipitation will occur if these agents are combined in the same infusion solution 1.

LEUCOVORIN CALCIUM FOR INJECTION

Usual adult and adolescent dose

Antidote (to folic acid antagonists)¾
To methotrexate (inadvertent overdose)¾
Intramuscular or intravenous, 10 mg (base) per square meter of body surface area every six hours until methotrexate blood concentrations fall to less than 5 ´ 10 -8 Molar.
Note:
If, at 24 hours following methotrexate administration, the serum creatinine is increased 50% over baseline or serum methotrexate is greater than 5 ´ 10 -6 Molar, the dose of leucovorin should be 100 mg (base) per square meter of body surface area every three hours intravenously until methotrexate concentrations are reduced to appropriate levels 1.

Only solutions prepared with sterile water for injection (i.e., without benzyl alcohol) should be used for doses greater than 10 mg per square meter of body surface area.

To pyrimethamine or trimethoprim¾
Prevention¾Intramuscular, 400 mcg (0.4 mg) to 5 mg (base) with each dose of the folic acid antagonist.
Treatment¾Intramuscular, 5 to 15 mg (base) per day.
Megaloblastic anemia, secondary to folate deficiency¾
Intramuscular, up to 1 mg (base) per day.
Carcinoma, colorectal (treatment adjunct) ¾
Intravenous, 200 mg per square meter of body surface area over a minimum of three minutes, followed by fluorouracil 370 mg per square meter of body surface area intravenously 1 , or
Intravenous, 20 mg per square meter of body surface area, followed by fluorouracil 425 mg per square meter of body surface area intravenously 1.

Either regimen is given daily for five days, and the course may be repeated at four-week intervals for two courses and then at four- to five-week intervals, as determined by toxicity to the previous course 1.

Note: Only solutions prepared with sterile water for injection (i.e., without benzyl alcohol) should be used, since the dose is greater than 10 mg per square meter of body surface area.
Because of its calcium content, leucovorin calcium for injection should be administered by intravenous injection slowly, at a rate that does not exceed 160 mg of leucovorin per minute. 1

Usual pediatric dose

Antidote (to folic acid antagonists) or
Megaloblastic anemia¾See Usual adult and adolescent dose .
Carcinoma, colorectal (treatment adjunct)¾Dosage has not been established.

Size(s) usually available:

U.S.¾50 mg (base) (Rx) [Generic] (without preservative)

100 mg (base) (Rx)[Wellcovorin (without preservative)] [Generic] (without preservative)

350 mg (base) (Rx) [Generic] (without preservative)

Canada¾50 mg (base) (Rx) [Generic] (without preservative)

100 mg (base) (Rx) [Generic] (without preservative)

350 mg (base) (Rx) [Generic] (without preservative)

Packaging and storage:

Prior to reconstitution, store below 40 °C (104 °F), preferably between 20 and 25 °C (68 and 77 °F), unless otherwise specified by manufacturer. Protect from light 1.

Preparation of dosage form:

Leucovorin calcium for injection is prepared for parenteral use by adding 5 or 10 mL of bacteriostatic water for injection (preserved with benzyl alcohol) to the vial containing 50 or 100 mg (base), respectively, producing a solution containing 10 mg per mL. If doses greater than 10 mg per square meter of body surface area are to be used, sterile water for injection should be used for reconstitution and the resulting solution used immediately 1.

Caution: Use of diluents containing benzyl alcohol is not recommended for preparation of medications for use in neonates. A fatal toxic syndrome consisting of metabolic acidosis, CNS depression, respiratory problems, renal failure, hypotension, and possibly seizures and intracranial hemorrhages has been associated with this use.

Stability:

Reconstituted solutions prepared with bacteriostatic water for injection (preserved with benzyl alcohol) should be used within 7 days 1.

Intravenous solutions containing leucovorin calcium in 10% dextrose injection, 10% dextrose in 0.9% sodium chloride injection, lactated Ringer's injection, or Ringer's injection have been found to maintain at least 90% of labeled potency when used within twenty-four hours.

Incompatibilities:

Leucovorin calcium for injection is incompatible with fluorouracil; precipitation will occur if these agents are combined in the same infusion solution 1.