

LEUCOVORIN CALCIUM leucovorin calcium injection, solution

Ingram Pharmaceuticals, LLC
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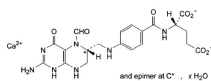
LEUCOVORIN CALCIUM INJECTION, USP

Rx ONLY

DESCRIPTION

Leucovorin is one of several active, chemically reduced derivatives of folic acid. It is useful as an antidote to drugs which act as folic acid antagonists.

Also known as folinic acid, Citrovorum factor, or 5-formyl-5,6,7,8-tetrahydrofolate, this compound has the chemical designation of L-Glutamic acid, N-(2,4,10-trimethyl-5-formyl-5,6,7,8-tetrahydro-2-imidazo[5,1-b]pyrimidin-6-ylamino)benzoyl-L-calcium salt (1:1). The structural formula of leucovorin calcium is:



Leucovorin Calcium Injection, USP is a sterile, preservative-free solution (injection and/or intravenous (IV) administration) in a 50 mL, single-dose vial. Each mL contains leucovorin calcium equivalent to 10 mg Leucovorin. USP 8 mg sodium chloride, sodium hydroxide and/or hydrochloric acid for pH adjustment pH 8.3 (6.5 to 8.5).

There is 0.044 mg of calcium per mg of leucovorin calcium. Solution contains no bacteriostats or antimicrobial agents.

CLINICAL PHARMACOLOGY

Leucovorin is a mixture of the diastereoisomers of the 5-formyl derivative of tetrahydrofolic acid (THF). The biologically active component of the mixture is the (4S)-isomer, known as Citrovorum factor or (2S)-folinic acid. Leucovorin does not require reduction by the enzyme dihydrofolate reductase in order to participate in reactions utilizing folates as a source of carbon skeletons. Leucovorin (5-formyltetrahydrofolate) is rapidly metabolized (via 5,10-methylenetetrahydrofolate, 5,10-methyltetrahydrofolate) to L-methyltetrahydrofolate. L-methyltetrahydrofolate can then be metabolized via other pathways back to 5,10-methylenetetrahydrofolate, which is converted to 5-methyltetrahydrofolate by methylenetetrahydrofolate reductase (enzyme deficiency causes the disease MTHFR) and NADPH.

Administration of leucovorin can counteract the therapeutic and toxic effects of folic acid antagonists such as methotrexate, which act by inhibiting dihydrofolate reductase.

In cancer, leucovorin can enhance the therapeutic and toxic effects of fluoropyrimidines used in cancer therapy, such as 5-fluorouracil. Concurrent administration of leucovorin does not appear to alter the plasma pharmacokinetics of 5-fluorouracil. 5-Fluorouracil is metabolized to fluorouridylic acid, which binds to and inhibits the enzyme thymidylate synthase (enzyme important in DNA repair and replication).

Leucovorin is readily converted to another reduced folate, 5,10-methylenetetrahydrofolate, which acts to stabilize the binding of fluorouridylic acid to thymidylate synthase and thereby enhances the inhibition of this enzyme.

The pharmacokinetics after intravenous, intramuscular and oral administration of a 25 mg dose of leucovorin were studied in male volunteers. After intravenous administration serum total reduced folates (as measured by Latex-biotin assay) reached a mean peak of 1250 ng/mL (range 850 to 1625) 70 minutes after administration. This total rise in reduced folates was primarily due to the parent compound 5-formyl-THF (measured by Spectroscan (lactulose assay) which rose to 1206 ng/mL at 30 minutes, 1 hour after parent compound followed and coincided with the appearance of the active metabolite 5-methyl-THF which became the predominant circulating form of the drug.

The mean peak of 5-methyl-THF was 20 mg/mL and occurred at 1.1 hours. The terminal half-life for leucovorin was 2.3 hours. The area under the curve and the area under the curve corrected for body surface area were 129.12 mg/mL-hr and 12.18 mg/mL-hr, respectively. The mean peak of 5-methyl-THF was 20 mg/mL at 2.8 hours. The terminal half-life of total reduced folates was 6.2 hours. There was no difference in statistical significance between oral and IV administration in the AUC for total reduced folates, 5-formyl-THF or 5-methyl-THF.

After intramuscular injection, the mean peak of serum total reduced folates was 436 ng/mL (range 240 to 725) and occurred at 23 minutes. Similar to IV administration, the initial sharp rise was due to the parent compound. The mean peak of 5-formyl-THF was 160 ng/mL and occurred at 20 minutes. The level of the metabolite 5-methyl-THF increased subsequently over time until at 1.5 hours it represented 26% of the circulating total folates. The mean peak of 5-methyl-THF was 20 mg/mL at 2.8 hours. The terminal half-life of total reduced folates was 6.2 hours. There was no difference in statistical significance between oral and IV administration in the AUC for total reduced folates, 5-formyl-THF or 5-methyl-THF.

After oral administration of leucovorin reconstituted with aseptic elixir, the mean peak concentration of serum total reduced folates was 303 ng/mL (range 100 to 550). The mean time to peak was 2.3 hours and the terminal half-life was 5.7 hours. The major component was the metabolite 5-methyltetrahydrofolate to which leucovorin is primarily converted in the intestinal mucosa. The mean peak of 5-methyl-THF was 387 ng/mL at 2.4 hours. The peak level of the parent compound was 14 ng/mL at 1.2 hours. The AUC of total reduced folates after oral administration of the 25 mg dose was 52% of the AUC after intravenous administration.

Following oral administration, leucovorin is rapidly absorbed and reaches the serum pool of reduced folates. At a dose of 25 mg, almost 100% of the folates but only 20% of the folates is absorbed.

Oral absorption of leucovorin is saturated at doses above 25 mg. The apparent bioavailability of leucovorin was 77% for 25 mg, 70% for 50 mg, and 37% for 100 mg.

In a randomized clinical study conducted by the Mayo Clinic and the North Central Cancer Treatment Group (Mayo-NCCCTG) in patients with advanced metastatic colorectal cancer, three treatment regimens were compared: Leucovorin (LV) 200 mg/m² and 5-Fluorouracil (5-FU) 370 mg/m² versus LV 20 mg/m² and 5-FU 425 mg/m² versus 5-FU 500 mg/m². All drugs were administered intravenously over 15 minutes every 5 days repeated every 28 to 35 days. Response rates were 20% (p=0.04) versus 5-FU alone 47% (p<0.001) versus 5-FU alone and 19% for the high-dose leucovorin, low-dose leucovorin and 5-FU dose regimens, respectively. Respective median survival times were 12.2 months (p=0.037), 12 months (p=0.05), and 7.7 months. The low-dose LV regimen gave a statistically significant improvement in weight gain of more than 5%, relief of symptoms, and improvement in performance status. The high-dose LV regimen gave a statistically significant improvement in performance status and trend toward improvement in weight gain and in relief of symptoms but these were not statistically significant.

In a second Mayo-NCCCTG randomized clinical study the 5-FU alone arm was replaced by a regimen of sequentially administered methotrexate (MTX), 5-FU, and LV. Response rates with LV 200 mg/m² and 5-FU 370 mg/m² versus LV 20 mg/m² and 5-FU 425 mg/m² versus sequential MTX and 5-FU and LV were respectively 35% (p=0.01), 42% (p<0.001) and 44%. Respective median survival times were 12.7 months (p=0.04), 12.7 months (p=0.01), and 8.4 months. No statistically significant difference in weight gained more than 5% or in improvement in performance status was seen between the treatment arms.

The pharmacokinetics of 200 mg doses of leucovorin administered intravenously and orally (reconstituted powder, not tablet) have been evaluated in healthy male subjects. The serum clearance corrected for bioavailability, arterial half-life, and apparent volume of distribution of total folates was not significantly different between routes of administration. The oral bioavailability of the 200 mg dose was 33%. Eighty three percent of the biologically active IV dose was recovered in the urine within 24 hours, 31% as 5-methyltetrahydrofolate. Twenty percent of the same oral dose was excreted in 24 hours, 19% as 5-methyltetrahydrofolate.

INDICATIONS AND USAGE

Leucovorin calcium is indicated after high-dose methotrexate therapy in oncogenesis.

Leucovorin calcium is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of methotrexate overdosage of folic acid antagonists.

Leucovorin calcium is indicated in the treatment of megaloblastic anemia due to folic acid deficiency when oral therapy is not feasible.

Leucovorin is also indicated for use in combination with 5-Fluorouracil in palliative therapy in the palliative treatment of patients with advanced colorectal cancer. Leucovorin should not be mixed in the same infusion as 5-Fluorouracil because a precipitate may form.

CONTRAINDICATIONS

Leucovorin is contraindicated for patients with severe anemia and other megaloblastic anemia secondary to the lack of vitamin B₁₂. A hematologic remission may occur while neurologic manifestations continue to progress.

WARNINGS

In the event of accidental overdosage of folic acid antagonists, intravenous leucovorin should be administered as promptly as possible. As the time interval between anticancer administration (e.g. methotrexate) and leucovorin rescue increases, leucovorin's effectiveness in counteracting toxicity decreases. In the event of accidental overdosage of immediately administered folic acid antagonists, do not administer leucovorin intradermally. LEUCOVORIN MAY BE HARMFUL OR FATAL, IF GIVEN INTRATELIVELY.

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

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute).

Leucovorin enhances the toxicity of 5-Fluorouracil. When these drugs are administered concurrently in the palliative therapy of advanced colorectal cancer, the dosage of 5-Fluorouracil must be lower than usually administered. Although toxic reactions observed in patients treated with the combination of leucovorin plus 5-Fluorouracil are qualitatively similar to those observed in patients treated with 5-Fluorouracil alone, gastrointestinal toxicity (particularly stomatitis and diarrhea) are observed more commonly and may be more severe and prolonged duration in patients treated with the combination.

In the first Mayo-NCCCTG controlled trial, toxicity, primarily gastrointestinal, resulted in 7% of patients requiring discontinuation when treated with 5-Fluorouracil alone or 5-Fluorouracil in combination with 200 mg/m² of leucovorin, 20% when treated with 5-Fluorouracil in combination with 20 mg/m² of leucovorin, and 26% in the second Mayo-NCCCTG trial. Hospitalizations related to treatment with 20 mg/m² also appear to occur more often in patients treated with the low dose leucovorin-5-fluorouracil combination than in patients treated with the high dose combination — 11% versus 3%. Therapy with leucovorin and 5-Fluorouracil must be initiated or continued in patients who have symptoms of gastrointestinal toxicity of any severity, until those symptoms have completely resolved. Patients with diarrhea should be treated with particular care until the diarrhea has resolved, as rapid clinical deterioration leading to death can occur. In an additional study utilizing higher weekly doses of 5-Fluorouracil and leucovorin, clearly elderly and/or debilitated patients were found to be at greater risk for severe gastrointestinal toxicity.

Seizures and/or syncope have been reported rarely in cancer patients receiving leucovorin, usually in association with fluoropyrimidine administration, and most commonly in those with CNS metastases or other predisposing factors; however, a causal relationship has not been established.

The concurrent 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 hematologic indices of methotrexate such as the myelotoxicity resulting from drug and/or metabolite participation in the kidney.

Since leucovorin enhances the toxicity of fluorouracil, leucovorin-5-fluorouracil combination therapy for advanced colorectal cancer should be administered under the supervision of a physician experienced in the use of anti-neoplastic cancer chemotherapy. Particular care should be taken in the treatment of elderly or debilitated colorectal cancer patients, as these patients may be at increased risk of severe toxicity.

Laboratory Tests

Patients being treated with the leucovorin-5-fluorouracil combination should have a CBC with differential and platelet plate to each treatment. During the first two courses a CBC with differential and platelets has to be repeated weekly and thereafter once a week at the start of each cycle. WBC nadir, erythrocytes and liver function tests should be performed prior to each treatment for the first three cycles thereafter in every other cycle. Dosage modifications of leucovorin should be made as follows, based on the most severe toxicity:

Diarrhea and/or Stomatitis	WBC/mm ³ Neutrophils	Platelets/mm ³ Neutrophils	5-FU dose
Mild/moderate	1,000 to 1,500	75 to 75,000	decrease 20%
Severe	<1,000	<25,000	decrease 50%

If no toxicity occurs, the 5-Fluorouracil dose may increase 10%. Treatment should be deferred until WBCs are 4,000/mm³ and platelets 130,000/mm³. 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 tumor progression.

Drug Interactions

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

Preclinical animal and human studies have shown that small quantities of systemically administered leucovorin (one the CSF primarily as 5-methyltetrahydrofolate and, in addition, remains 10 fold less of magnitude lower than the usual methotrexate concentrations following intrathecal administration). However, high doses of leucovorin reduce the efficacy of intrathecally administered methotrexate. Leucovorin may enhance the toxicity of 5-Fluorouracil (see WARNINGS).

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Adverse 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 PRECAUTIONS, Drug Interactions.

Geriatric Use

Clinical studies of leucovorin calcium did not show differences in safety or effectiveness between subjects over 65 and younger subjects. Other clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some elderly patients cannot be ruled out. This drug is known to be excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

Allergic sensitization, including anaphylactic reactions and urticaria, has been reported following the

administration of both oral and parenteral leucovorin. No other adverse reactions have been attributed to the use of leucovorin per se.

Table 1 summarizes significant adverse events occurring in 101 patients treated with the leucovorin/5-fluorouracil combination compared against 70 patients treated with 5-fluorouracil alone for advanced colorectal carcinoma. These data are taken from the Mayo/NCCCT large multicenter prospective trial evaluating the efficacy and safety of the combination regimen.

Table 1: PERCENTAGE OF PATIENTS TREATED WITH LEUCOVORIN/FLOUROURACIL FOR ADVANCED COLORECTAL CARCINOMA REPORTING ADVERSE EXPERIENCES OR HOSPITALIZED FOR TOXICITY

	(High LV*) 5FU		(Low LV*) 5FU		5-FU Alone	
	N=155	Grade 3+† 3Ag‡	N=161	Grade 3+ 3Ag‡	N=70	Grade 3+ †
	Age‡	%	%	%	%	%
Leukopenia	69	14	83	23	93	48
Thrombocytopenia	8	2	8	1	18	2
Infection	8	1	3	1	7	2
Nausea	74	15	60	9	60	6
Vomiting	46	8	44	9	40	7
Diarrhea	66	13	67	14	43	11
Stomatitis	75	15	84	29	59	16
Constipation	3	0	4	0	1	-
Laboratory Malaise	13	3	12	2	6	3
Fatigue	42	5	43	6	37	7
Dermatitis	21	2	25	1	13	-
Asthenia	14	1	22	4	14	-
Hospitalization	5%		15%		7%	

* High LV = Leucovorin 200 mg/m²

† Low LV = Leucovorin 20 mg/m²

‡ Age = percentage of patients reporting toxicity of any severity

§ Grade 3+ = percentage of patients reporting toxicity of Grade 3 or higher

To report SUSPECTED ADVERSE REACTIONS, contact Ingress Pharmaceuticals, LLC at 1-877-743-1978 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

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

DOSEAGE AND ADMINISTRATION

Advanced Colorectal Cancer

Either of the following two regimens is recommended:

1. Leucovorin is administered at 200 mg/m² by slow intravenous injection over a minimum of 3 minutes, followed by 5-fluorouracil at 570 mg/m² by intravenous injection.

2. Leucovorin is administered at 20 mg/m² by intravenous injection followed by 5-fluorouracil at 425 mg/m² by intravenous injection.

5-Fluorouracil and leucovorin should be administered separately to avoid the formation of a precipitate. Treatment is repeated daily for five days. This five-day treatment course may be repeated at 4 week (28-day) intervals, for 2 courses and then repeated at 4 to 5 week (28 to 35 day) intervals provided that the patient has completely 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 hematologic or gastrointestinal toxicity in the prior treatment course, and by 50% for patients who experienced severe toxicity (see PRECAUTIONS: Laboratory Tests). For patients who experienced no toxicity in the prior treatment course, 5-fluorouracil dosages may be increased by 10%. Leucovorin dosages are not adjusted for toxicity.

Leucovorin Rescue After High-Dose Methotrexate Therapy

The recommendations for leucovorin rescue are based on a methotrexate dose of 12 to 15 grams/m² administered by intravenous infusion over 4 hours (see methotrexate package insert for full prescribing information).

Leucovorin rescue at a dose of 15 mg (approximately 10 mg/m²) every 6 hours for 10 doses starts 24 hours after the beginning of the methotrexate infusion. In the presence of gastrointestinal toxicity, nausea or vomiting, leucovorin should be administered parenterally. Do not administer leucovorin intrathecally.

Serum creatinine and methotrexate levels should be determined at least once daily. Leucovorin administration, hydration, and urinary alkalization (pH of 7.0 or greater) should be continued until the methotrexate level is below 5 x 10⁻⁶ M (0.05 micromolar). The leucovorin dose should be adjusted or leucovorin treatment extended based on the guidelines provided in below table.

Table 2: GUIDELINES FOR LEUCOVORIN DOSEAGE AND ADMINISTRATION DO NOT ADMINISTER LEUCOVORIN INTRATHECALLY

Clinical Situation	Laboratory Findings	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 q 6 hours for 60 hours (10 doses starting at 24 hours after start of methotrexate infusion).
Delayed Late Methotrexate Elimination	Serum methotrexate level remaining above 0.2 micromolar at 72 hours, and more than 0.05 micromolar 96 hours after administration.	Continue 15 mg PO, IM, or IV q 6 hours, until methotrexate level is less than 0.05 micromolar.
Delayed Early Methotrexate Elimination and/or Evidence of Acute Renal Injury	Serum methotrexate level of 50 micromolar or more at 24 hours, or 5-micromolar or more at 48 hours after administration OR a 100% or greater increase in serum creatinine level at 24 hours after methotrexate administration (e.g., an increase from 0.5 mg/dL to a level of 1 mg/dL, or more) OR more than 100 mg IV q 3 hours, until methotrexate level is less than 0.05 micromolar.	Continue 15 mg PO, IM, or IV q 6 hours, until methotrexate level is less than 0.05 micromolar, then 15 mg IV q 3 hours until methotrexate level is less than 0.05 micromolar.

Patients who experience delayed early methotrexate elimination are likely to develop reversible renal failure. In addition to appropriate leucovorin therapy, these patients require continuing hydration and urinary alkalization, 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 abnormalities described in the table above. These abnormalities may or may not be associated with significant clinical toxicity. If significant toxicity is observed, leucovorin rescue should be extended for an additional 24 hours (total of 4 doses over 84 hours) in subsequent courses of therapy. The possibility that the patient is taking other oral or intravenous drugs which interact with methotrexate (e.g., oral contraceptives which may interfere with the renal tubular secretion of methotrexate) should always be reconsidered when laboratory abnormalities or clinical toxicities are observed.

Impaired Methotrexate Elimination or Inadequate Overdose

Leucovorin rescue should begin as soon as possible after an inadequate overdose and within 24 hours of methotrexate administration when there is delayed recretion (see WARNINGS). Leucovorin 10 mg/m² should be administered IV, IM, or PO every 6 hours until the serum methotrexate level is less than 10⁻⁶ M. In the presence of acute renal insufficiency, nausea, or vomiting, leucovorin should be administered parenterally. In all subsequent treatment courses, 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 20% 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 5 x 10⁻⁶ M, the dose of leucovorin should be increased to 100 mg/m² IV every 3 hours until the methotrexate level is less than 10⁻⁶ M.

Hydration 2 L and urinary alkalization with sodium bicarbonate solution should be employed concurrently. The bicarbonate dose should be adjusted to maintain the urine pH at 7.0 or greater.

Metabolic Harm Due to Folic Acid Deficiency

Up to 1 mg daily. There is 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.

Because of the calcium content of the leucovorin solution, no more than 160 mg of leucovorin should be injected intravenously per minute (16 mL of a 10 mg/mL, or 8 mL of a 20 mg/mL solution per minute).

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Leucovorin should not be added to the same infusion as 5-Fluorouracil, since this may lead to the formation of a precipitate.

HOW SUPPLIED

Leucovorin Calcium Injection USP, 500 mg/50 mL (10 mg/mL) is clear, colorless solution to yellow solution supplied in a 50 mL, neutral, single-dose vial as follows:

NDC 58742-464-58 500 mg individually boxed.

Store at refrigerated 2° to 8°C (36° to 46°F). Protect from light. Discard unused portion. Retain in container until time of use.

REFERENCES

1. McGuire B, Sia L, Hayes J, et al. "Absorption kinetics of orally administered Leucovorin Calcium," NCI Monograph 1987:5-47-56.

Manufactured for:

Ingress Pharmaceuticals, LLC
Ocala, FL 32676-6488
Made in Switzerland.

Revised: 07/2018

PACKAGE LABEL/PRINCIPAL DISPLAY PANEL



LEUCOVORIN CALCIUM			
Leucovorin Calcium Injection, solution			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	NDA Code (Number)	108-167-101-014
Route of Administration	INTRAVENOUS, INTRAMUSCULAR		
Active Ingredient/Active Moiety			
	Ingredient Name	Brand Strength	Strength
	LEUCOVORIN CALCIUM (LEUCOVORIN) (LEUCOVORIN) (UNQ17) (D01AA01)	LEUCOVORIN	10 mg, 1 mL
Inactive Ingredients			
	Ingredient Name		Strength
	ACETIC ACID (D01AC02)		7 mg, 1 mL
	ACETIC ACID SODIUM SALT (D01AC02)		
	ACETIC ACID SODIUM SALT (D01AC02)		
	ACETIC ACID SODIUM SALT (D01AC02)		
Packaging			
#	Item Code	Package Description	Marketing Start Date
1	108-167-101-014	10 x 1 CARTON	10/2018
1		50 x 1 VIAL, SINGLE DOSE, Type 9, Sterile Cartridge	
Marketing Information			
Marketing Category	(Application Number or Marketing Classification)	Marketing Start Date	Marketing End Date
NDA	108-167-101-014	10/2018	
Labeler - Ingress Pharmaceuticals, LLC (0122617)			
Manufacturer - Ingress Pharmaceuticals, LLC (0122617)			
Establishment			
Name	Address	Business Operation	
Ingress Pharmaceuticals, LLC	28720 137	MANUFACTURE	
0000	28720 137	MANUFACTURE	

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Ingress Pharmaceuticals, LLC