

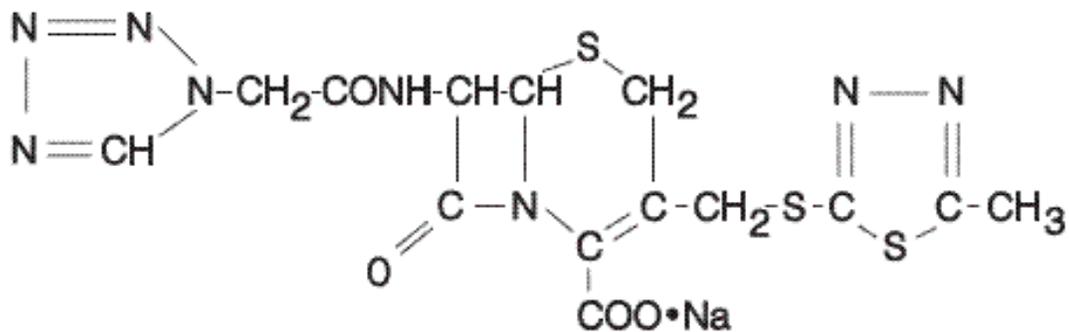
Cefazolin Injection, USP in GALAXY Container (PL 2040 Plastic)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Cefazolin Injection, USP and other antibacterial drugs, Cefazolin Injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION

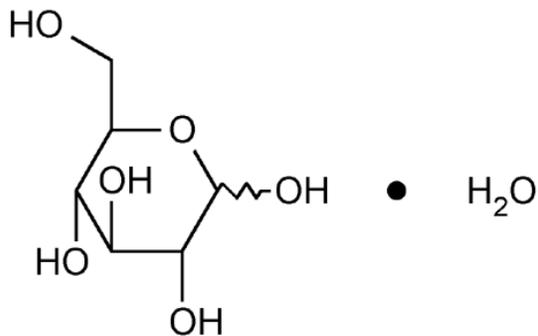
Cefazolin Injection, USP is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of (6*R*,7*R*)-3-[[[5-methyl-1,3,4-thiadiazol-2-yl)thio]methyl]-8-oxo-7-[2-(1*H*-tetrazol-1-yl)acetamido]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Structural Formula:



The sodium content is 46 mg per gram of cefazolin.

Dextrose Hydrated, USP structural (molecular) formula:



The molecular weight of Dextrose Hydrus, USP is 198.17.

The chemical name is D-Glucose, Monohydrate.

Cefazolin Injection, USP is a frozen, premixed, iso-osmotic, sterile, nonpyrogenic 50 mL solution containing cefazolin sodium equivalent to 1 g of Cefazolin, USP. Dextrose, USP has been added to adjust osmolality (2 g as dextrose hydrus).

The pH of Cefazolin Injection, USP has been adjusted with sodium bicarbonate. The solution is intended for intravenous use after thawing to room temperature.

This GALAXY container (PL 2040 Plastic) is fabricated from a specially designed multilayer plastic (PL 2040). Solutions are in contact with the polyethylene layer of this container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. However, the suitability of the plastic has been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

Studies have shown that following intravenous administration of cefazolin to normal volunteers, mean serum concentrations peaked at approximately 185 mcg/mL and were approximately 4 mcg/mL at 8 hours for a 1-gram dose.

The serum half-life for cefazolin is approximately 1.8 hours following intravenous administration.

In a study (using normal volunteers) of constant intravenous infusion with dosages of 3.5 mg/kg for 1 hour (approximately 250 mg) and 1.5 mg/kg the next 2 hours (approximately

100 mg), cefazolin produced a steady serum level at the third hour of approximately 28 mcg/mL.

Studies in patients hospitalized with infections indicate that cefazolin produces mean peak serum levels approximately equivalent to those seen in normal volunteers.

Bile levels in patients without obstructive biliary disease can reach or exceed serum levels by up to 5 times; however, in patients with obstructive biliary disease, bile levels of cefazolin are considerably lower than serum levels (<1.0 mcg/mL).

In synovial fluid, the level of cefazolin becomes comparable to that reached in serum at about 4 hours after drug administration.

Studies of cord blood show prompt transfer of cefazolin across the placenta. Cefazolin is present in very low concentrations in the milk of nursing mothers.

Cefazolin is excreted unchanged in the urine. In the first 6 hours approximately 60% of the drug is excreted in the urine and this increases to 70% to 80% within 24 hours.

In patients undergoing peritoneal dialysis (2 L/hr.), cefazolin produced mean serum levels of approximately 10 and 30 mcg/mL after 24 hours instillation of a dialyzing solution containing 50 mg/L and 150 mg/L, respectively. Mean peak levels were 29 mcg/mL (range 13 to 44 mcg/mL) with 50 mg/L (3 patients), and 72 mcg/mL (range 26 to 142 mcg/mL) with 150 mg/L (6 patients). Intraperitoneal administration of cefazolin is usually well tolerated.

Controlled studies on adult normal volunteers, receiving 1 gram 4 times a day for 10 days, monitoring CBC, SGOT, SGPT, bilirubin, alkaline phosphatase, BUN, creatinine, and urinalysis, indicated no clinically significant changes attributed to cefazolin.

Microbiology

Mechanism of Action

Cefazolin is a bactericidal agent that acts by inhibition of bacterial cell wall synthesis.

Resistance

Predominant mechanisms of bacterial resistance to cephalosporins include the presence of extended-spectrum beta-lactamases and enzymatic hydrolysis.

Antimicrobial Activity

Cefazolin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in **INDICATIONS AND USAGE**.

Gram-Positive Bacteria

Staphylococcus aureus

Staphylococcus epidermidis

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

Methicillin-resistant staphylococci are uniformly resistant to cefazolin.

Gram-Negative Bacteria

Escherichia coli

Proteus mirabilis

Most isolates of indole positive *Proteus* (*Proteus vulgaris*), *Enterobacter* spp., *Morganella morganii*, *Providencia rettgeri*, *Serratia* spp., and *Pseudomonas* spp. are resistant to cefazolin.

Susceptibility Test Methods

For specific information regarding susceptibility test interpretive criteria and associated text methods and quality control standards recognized by FDA for this drug, please see: <http://www.fda.gov/STIC>.

INDICATIONS AND USAGE

Cefazolin Injection, USP is indicated in the treatment of the following infections due to susceptible organisms:

Respiratory Tract Infections: Due to *S. pneumoniae*, *Klebsiella* species, *H. influenzae*, *S. aureus* (penicillin sensitive and penicillin resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Cefazolin is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of cefazolin in the subsequent prevention of rheumatic fever are not available.

Urinary Tract Infections: Due to *E. coli*, *P. mirabilis*, *Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and Skin Structure Infections: Due to *S. aureus* (penicillin sensitive and penicillin-resistant), group A beta-hemolytic streptococci, and other strains of streptococci.

Biliary Tract Infections: Due to *E. coli*, various strains of streptococci, *P. mirabilis*, *Klebsiella* species, and *S. aureus*.

Bone and Joint Infections: Due to *S. aureus*.

Genital Infections: (*i.e.*, prostatitis, epididymitis) due to *E. coli*, *P. mirabilis*, *Klebsiella* species, and some strains of enterococci.

Septicemia: Due to *S. pneumoniae*, *S. aureus* (penicillin sensitive and penicillin resistant), *P. mirabilis*, *E. coli*, and *Klebsiella* species.

Endocarditis: Due to *S. aureus* (penicillin sensitive and penicillin resistant), and group A beta-hemolytic streptococci.

Perioperative Prophylaxis: The prophylactic administration of cefazolin preoperatively, intraoperatively, and postoperatively may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures which are classified as contaminated or potentially contaminated (*e.g.*, vaginal hysterectomy, and cholecystectomy in high-risk patients such as those older than 70 years, with acute cholecystitis, obstructive jaundice, or common duct bile stones).

The perioperative use of cefazolin may also be effective in surgical patients in whom infection at the operative site would present a serious risk (*e.g.*, during open-heart surgery and prosthetic arthroplasty).

The prophylactic administration of cefazolin should usually be discontinued within a 24-hour period after the surgical procedure. In surgery where the occurrence of infection may be particularly devastating (*e.g.*, open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cefazolin may be continued for 3 to 5 days following the completion of surgery.

If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism so that appropriate therapy may be instituted (see **DOSAGE AND ADMINISTRATION**).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of cefazolin and other antibacterial drugs, cefazolin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

CEFAZOLIN IS CONTRAINDICATED IN PATIENTS WITH KNOWN ALLERGY TO THE CEPHALOSPORIN GROUP OF ANTIBIOTICS.

Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

WARNINGS

BEFORE THERAPY WITH CEFAZOLIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFAZOLIN, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO CEFAZOLIN OCCURS, DISCONTINUE TREATMENT WITH THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefazolin, and may range in severity from mild to life-threatening.

Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of “antibiotic associated colitis.”

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an oral antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS

General

Prolonged use of cefazolin may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When cefazolin is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see **DOSAGE AND ADMINISTRATION**).

As with other beta-lactam antibiotics, seizures may occur if inappropriately high doses are administered to patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**).

Cefazolin, as with all cephalosporins, should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Cephalosporins may be associated with a fall in prothrombin activity. Those at risk include patients with renal or hepatic impairment or poor nutritional state, as well as patients receiving a protracted course of antimicrobial therapy, and patients previously stabilized on anticoagulant therapy. Prothrombin time should be monitored in patients at risk and exogenous vitamin K administered as indicated.

As with other dextrose-containing solutions, Cefazolin Injection, USP should be prescribed with caution in patients with overt or known subclinical diabetes mellitus or carbohydrate intolerance for any reason.

Prescribing cefazolin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Drug Interactions

Probenecid may decrease renal tubular secretion of cephalosporins when used concurrently, resulting in increased and more prolonged cephalosporin blood levels.

Drug/Laboratory Test Interactions

A false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution or with CLINITEST tablets, but not with enzyme-based tests such as CLINISTIX Kit.

Positive direct and indirect antiglobulin (Coombs) tests have occurred; these may also occur in neonates whose mothers received cephalosporins before delivery.

Information for Patients

Patients should be counseled that antibacterial drugs including cefazolin should only be used to treat bacterial infections. They do not treat viral infections (*e.g.*, the common cold). When cefazolin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by cefazolin or other antibacterial drugs in the future.

Carcinogenesis/Mutagenesis

Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of cefazolin have not been performed.

Pregnancy

Teratogenic Effects

Reproduction studies have been performed in rats, mice, and rabbits at doses up to 25 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefazolin. There are, however, no adequate and well-controlled studies in

pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

When cefazolin has been administered prior to caesarean section, drug levels in cord blood have been approximately one quarter to one third of maternal drug levels. The drug appears to have no adverse effect on the fetus.

Nursing Mothers

Cefazolin is present in very low concentrations in the milk of nursing mothers. Caution should be exercised when cefazolin is administered to a nursing woman.

Pediatric Use

Safety and effectiveness for use in premature infants and neonates have not been established. See **DOSAGE AND ADMINISTRATION** for recommended dosage in pediatric patients older than 1 month.

Geriatric Use

Of the 920 subjects who received cefazolin in clinical studies, 313 (34%) were 65 years and over, while 138 (15%) were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially 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 (see **PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The following reactions have been reported:

Gastrointestinal

Diarrhea, oral candidiasis (oral thrush), vomiting, nausea, stomach cramps, anorexia, and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur

during or after antibiotic treatment (see **WARNINGS**). Nausea and vomiting have been reported rarely.

Allergic

Anaphylaxis, eosinophilia, itching, drug fever, skin rash, Stevens-Johnson syndrome.

Hematologic

Neutropenia, leukopenia, thrombocytopenia, thrombocythemia.

Hepatic

Transient rise in SGOT, SGPT, and alkaline phosphatase levels has been observed. As with other cephalosporins, reports of hepatitis have been received.

Renal

As with other cephalosporins, reports of increased BUN and creatinine levels, as well as renal failure, have been received.

Local Reactions

Rare instances of phlebitis have been reported at site of injection. Some induration has occurred.

Other Reactions

Genital and anal pruritus (including vulvar pruritus, genital moniliasis, and vaginitis).

To report SUSPECTED ADVERSE EVENTS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DOSAGE AND ADMINISTRATION

Note: Cefazolin Injection, USP in GALAXY Container (PL 2040 Plastic) is intended for intravenous infusion.

Usual Adult Dosage:

Type of Infection	Dose	Frequency
Moderate to severe infections	500 mg to 1 gram	every 6 to 8 hrs.
Mild infections caused by susceptible gram-positive cocci	250 mg to 500 mg	every 8 hours
Acute, uncomplicated urinary tract infections	1 gram	every 12 hours

Pneumococcal pneumonia	500 mg	every 12 hours
Severe, life-threatening infections (<i>e.g.</i> , endocarditis, septicemia)*	1 gram to 1.5 grams	every 6 hours

*In rare instances, doses of up to 12 grams of cefazolin per day have been used.

Perioperative Prophylactic Use

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are:

- a. 1 gram intravenously administered ½ hour to 1 hour prior to start of surgery.
- b. For lengthy operative procedures (*e.g.*, 2 hours or more), 500 mg to 1 gram intravenously administered during surgery (administration modified depending on the duration of the operative procedure).
- c. 500 mg to 1 gram intravenously administered every 6 to 8 hours for 24 hours postoperatively.

It is important that (1) the preoperative dose be given just (½ to 1 hour) prior to start of surgery so that adequate antibiotic levels are present in the serum and tissues at the time of initial surgical incision; and (2) cefazolin be administered, if necessary, at appropriate intervals during surgery to provide sufficient levels of the antibiotic at the anticipated moments of greatest exposure to infective organisms.

In surgery where the occurrence of infection may be particularly devastating (*e.g.*, open-heart surgery and prosthetic arthroplasty), the prophylactic administration of cefazolin may be continued for 3 to 5 days following the completion of surgery.

Dosage Adjustment for Patients With Reduced Renal Function

Cefazolin may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 mL/min. or greater or a serum creatinine of 1.5 mg % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 mL/min. or serum creatinine of 1.6 to 3.0 mg % can also be given full doses but dosage should be restricted to at least 8 hour intervals. Patients with creatinine clearance rates of 11 to 34 mL/min. or serum creatinine of 3.1 to 4.5 mg % should be given ½ the usual dose every 12 hours. Patients with creatinine clearance rates of 10 mL/min. or less or serum creatinine of 4.6 mg % or greater should be given ½ the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection. Patients undergoing peritoneal dialysis: See **CLINICAL PHARMACOLOGY**.

Pediatric Dosage

In pediatric patients, a total daily dosage of 25 to 50 mg per kg (approximately 10 to 20 mg per pound) of body weight, divided into 3 or 4 equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg per kg (45 mg per pound) of body weight for severe infections. Since safety for use in premature infants and in neonates has not been established, the use of cefazolin in these patients is not recommended.

Pediatric Dosage Guide					
Weight		25 mg/kg/day		25 mg/kg/day	
		Divided into 3 Doses		Divided into 4 Doses	
Lbs	Kg	Approximate Single Dose mg/q8h	Vol. (mL)	Approximate Single Dose mg/q6h	Vol. (mL)
			needed with dilution of 125 mg/mL		needed with dilution of 125 mg/mL
10	4.5	40 mg	0.35 mL	30 mg	0.25 mL
20	9.0	75 mg	0.60 mL	55 mg	0.45 mL
30	13.6	115 mg	0.90 mL	85 mg	0.70 mL
40	18.1	150 mg	1.20 mL	115 mg	0.90 mL
50	22.7	190 mg	1.50 mL	140 mg	1.10 mL

Weight		50 mg/kg/day		50 mg/kg/day	
		Divided into 3 Doses		Divided into 4 Doses	
Lbs	Kg	Approximate Single Dose mg/q8h	Vol. (mL)	Approximate Single Dose mg/q6h	Vol. (mL)
			needed with dilution of 225 mg/mL		needed with dilution of 225 mg/mL
10	4.5	75 mg	0.35 mL	55 mg	0.25 mL
20	9.0	150 mg	0.70 mL	110 mg	0.50 mL
30	13.6	225 mg	1.00 mL	170 mg	0.75 mL
40	18.1	300 mg	1.35 mL	225 mg	1.00 mL
50	22.7	375 mg	1.70 mL	285 mg	1.25 mL

In pediatric patients with mild to moderate renal impairment (creatinine clearance of 70 to 40 mL/min.), 60 percent of the normal daily dose given in equally divided doses every 12 hours should be sufficient. In patients with moderate impairment (creatinine clearance of 40 to 20 mL/min.), 25 percent of the normal daily dose given in equally divided doses

every 12 hours should be adequate. Pediatric patients with severe renal impairment (creatinine clearance of 20 to 5 mL/min.) may be given 10 percent of the normal daily dose every 24 hours. All dosage recommendations apply after an initial loading dose.

DIRECTIONS FOR USE OF CEFAZOLIN INJECTION, USP IN GALAXY CONTAINER (PL 2040 PLASTIC)

Cefazolin Injection, USP in GALAXY Container (PL 2040 Plastic) is to be administered either as a continuous or intermittent infusion using sterile equipment.

Storage

Store in a freezer capable of maintaining a temperature of -20°C (-4°F).

Thawing of Plastic Container

Thaw frozen container at room temperature (25°C/ 77°F) or under refrigeration (5°C/41°F). **(DO NOT FORCE THAW BY IMMERSION IN WATER BATHS OR BY MICROWAVE IRRADIATION.)**

Check for minute leaks by squeezing container firmly. If leaks are detected, discard solution as sterility may be impaired.

Do not add supplementary medication.

The container should be visually inspected. Visually inspect the container. If the outlet port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired. Components of the solution may precipitate in the frozen state and will dissolve upon reaching room temperature with little or no agitation. Potency is not affected. Agitate after solution has reached room temperature. If after visual inspection the solution remains cloudy or if an insoluble precipitate is noted or if any seals or outlet ports are not intact, the container should be discarded.

The thawed solution is stable for 30 days under refrigeration (5°C/41°F) and 48 hours at 25°C/77°F. **Do not refreeze thawed antibiotics.**

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration

1. Suspend container from eyelet support.
2. Remove protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

HOW SUPPLIED/STORAGE AND HANDLING

As with other cephalosporins, cefazolin tends to darken depending on storage conditions; within the stated recommendations, however, product potency is not adversely affected.

Cefazolin Injection, USP is supplied as a premixed frozen iso-osmotic solution in 50 mL single dose GALAXY plastic containers as follows:

2G3503	NDC 0338-3503-41	1 g cefazolin in 50 mL	Supplied 24/case
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Store at or below -20°C/-4°F. [See **DIRECTIONS FOR USE OF CEFAZOLIN INJECTION, USP IN GALAXY CONTAINER (PL 2040 PLASTIC).**]

Handle frozen product containers with care. Product containers may be fragile in the frozen state.

Rx Only

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