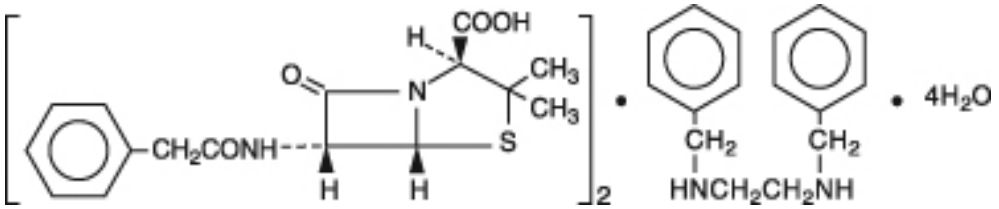
Bicillin® L-A
(penicillin G benzathine injectable suspension)
Disposable Syringe

Description

Bicillin L-A (penicillin G benzathine injectable suspension) is available for deep intramuscular injection. Penicillin G benzathine is prepared by the reaction of dibenzylethylene diamine with two molecules of penicillin G. It is chemically designated as (2*S*, 5*R*, 6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with *N,N'* -dibenzylethylenediamine (2:1), tetrahydrate. It occurs as a white, crystalline powder and is very slightly soluble in water and sparingly soluble in alcohol. Its chemical structure is as follows:



Bicillin L-A contains penicillin G benzathine in aqueous suspension with sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben.

Bicillin L-A suspension in the disposable-syringe formulation is viscous and opaque. It is available in a 1 mL, 2 mL, and 4 mL sizes containing the equivalent of 600,000, 1,200,000 and 2,400,000 units respectively of penicillin G as the benzathine salt. Read CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections prior to use.

CLINICAL PHARMACOLOGY

General

Penicillin G benzathine has an extremely low solubility and, thus, the drug is slowly released from intramuscular injection sites. The drug is hydrolyzed to penicillin G. This combination of hydrolysis and slow absorption results in blood serum levels much lower but much more prolonged than other parenteral penicillins.

Intramuscular administration of 300,000 units of penicillin G benzathine in adults results in blood levels of 0.03 to 0.05 units per mL, which are maintained for 4 to 5 days. Similar blood levels may persist for 10 days following administration of 600,000 units and for 14 days following administration of 1,200,000 units. Blood concentrations of 0.003 units per mL may still be detectable 4 weeks following administration of 1,200,000 units.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin, and intestines. Penicillin G penetrates into all other tissues and the spinal fluid to a lesser degree. With normal kidney function, the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

Microbiology

Mechanism of Action

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall peptidoglycan, rendering the cell wall osmotically unstable.

Mechanism of Resistance

Penicillin is not active against penicillinase-producing bacteria or against organisms resistant to beta-lactams because of alterations in the penicillin-binding proteins. Resistance to penicillin G has not been reported in *Streptococcus pyogenes*.

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

Gram-positive bacteria

Beta-hemolytic streptococci (groups A, B, C, G, H, L and M)

Other microorganisms
Treponema pallidum
Treponema carateum

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure.[10,11] The MIC values should be interpreted according to the following criteria:

Diffusion techniques

Quantitative methods that require the measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone

size should be determined using a standardized test method.[11,12] This procedure uses paper discs impregnated with 10 units penicillin to test the susceptibility of microorganisms to penicillin G benzathine injectable solution. The disc diffusion interpretive criteria are provided in the table below.

Streptococcus pyogenes (Group A)

Susceptibility Test Interpretive Criteria for Penicillin

	MIC (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	**Susceptible (S)**	**Intermediate (I)**	**Resistant (R)**	**Susceptible (S)**	**Intermediate (I)**	**Resistant (R)**
Streptococcus pyogenes[a,b]	≤ 0.12	-	-	≥ 24	-	-

[a]Susceptibility testing of penicillins for treatment of β–hemolytic streptococcal infections need not be performed routinely, because non-susceptible isolates are extremely rare in any β-hemolytic streptococcus and have not been reported from *Streptococcus pyogenes*. Any β - hemolytic streptococcal isolate found to be non-susceptible to penicillin should be re-identified, retested, and, if confirmed, submitted to a public health authority.[10,11]
[b]The lack of data precludes defining any other interpretive criteria than 'susceptible'.

Quality Control

Standardized susceptibility test procedure require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test.[10,11,12] Standard penicillin powder should provide the range of MIC values noted in the following table . For the diffusion technique using the 10 unit penicillin disc, the criteria in the following table should be achieved.

Acceptable Quality Control Ranges for Penicillin

QC Strain	MIC (mcg/ml)	Disc Diffusion (zone diameter in mm)
Streptococcus pneumoniae ATCC 49619	0.25-1	24 - 30

ATCC = American Type Culture Collection

INDICATIONS AND USAGE

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

Intramuscular penicillin G benzathine is indicated in the treatment of infections due to penicillin-G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine:

Mild-to-moderate infections of the upper-respiratory tract due to susceptible streptococci.

Venereal infections—Syphilis, yaws, bejel, and pinta.

Medical Conditions in which Penicillin G Benzathine Therapy is indicated as Prophylaxis:

Rheumatic fever and/or chorea—Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as follow-up prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

CONTRAINDICATIONS

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

WARNINGS

WARNING: NOT FOR INTRAVENOUS USE. DO NOT INJECT INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. THERE HAVE BEEN REPORTS OF INADVERTENT INTRAVENOUS ADMINISTRATION OF PENICILLIN G BENZATHINE WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION sections of the labeling.

Penicillin G benzathine should only be prescribed for the indications listed in this insert.

Anaphylaxis

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH BICILLIN L-A, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, BICILLIN L-A SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Bicillin L-A, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Method of Administration

Do not inject into or near an artery or nerve.

Injection into or near a nerve may result in permanent neurological damage.

Inadvertent intravascular administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Bicillin L-A and other penicillin preparations has resulted in severe neurovascular damage, including transverse myelitis with permanent paralysis, gangrene requiring amputation of digits and more proximal portions of extremities, and necrosis and sloughing at and surrounding the injection site. Such severe effects have been reported following injections into the buttock, thigh, and deltoid areas. Other serious complications of suspected intravascular administration which have been reported include immediate pallor, mottling, or cyanosis of the extremity both distal and proximal to the injection site, followed by bleb formation; severe edema requiring anterior and/or posterior compartment fasciotomy in the lower extremity. The above-described severe effects and complications have most often occurred in infants and small children. Prompt consultation with an appropriate specialist is indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection.[1-9] (See PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections.)

Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. (See DOSAGE AND ADMINISTRATION section.)

Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh.

PRECAUTIONS

General

Prescribing Bicillin L-A 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 a development of drug-resistant bacteria.

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Care should be taken to avoid intravenous or intra-arterial administration, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage. (See WARNINGS, and DOSAGE AND ADMINISTRATION sections.)

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

Information for Patients

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be counseled that antibacterial drugs including Bicillin L-A should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Bicillin L-A 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 Bicillin L-A or other antibacterial drugs in the future.

Laboratory Tests

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and concurrent use of these drugs should be avoided.

Concurrent administration of penicillin and probenecid increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

Pregnancy Category B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Soluble penicillin G is excreted in breast milk. Caution should be exercised when penicillin G benzathine is administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been conducted with this drug.

Pediatric Use

(See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections.)

Geriatric Use

Clinical studies of penicillin G benzathine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. 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 (see CLINICAL PHARMACOLOGY). 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

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

As with other treatments for syphilis, the Jarisch-Herxheimer reaction has been reported.

The following have been reported with parenteral penicillin G:

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia, and prostration); and anaphylaxis including shock and death. Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, penicillin G should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to therapy with penicillin G. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Gastrointestinal: Pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See WARNINGS section.)

Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurologic: Neuropathy.

Urogenital: Nephropathy.

The following adverse events have been temporally associated with parenteral administration of penicillin G benzathine:

Body as a Whole: Hypersensitivity reactions including allergic vasculitis, pruritus, fatigue, asthenia, and pain; aggravation of existing disorder; headache.

Cardiovascular: Cardiac arrest; hypotension; tachycardia; palpitations; pulmonary hypertension; pulmonary embolism; vasodilation; vasovagal reaction; cerebrovascular accident; syncope.

Gastrointestinal: Nausea, vomiting; blood in stool; intestinal necrosis.

Hemic and Lymphatic: Lymphadenopathy.

Injection Site: Injection site reactions including pain, inflammation, lump, abscess, necrosis, edema, hemorrhage, cellulitis, hypersensitivity, atrophy, ecchymosis, and skin ulcer. Neurovascular reactions including warmth, vasospasm, pallor, mottling, gangrene, numbness of the extremities, cyanosis of the extremities, and neurovascular damage.

Metabolic: Elevated BUN, creatinine, and SGOT.

Musculoskeletal: Joint disorder; periostitis; exacerbation of arthritis; myoglobinuria; rhabdomyolysis.

Nervous System: Nervousness; tremors; dizziness; somnolence; confusion; anxiety; euphoria; transverse myelitis; seizures; coma. A syndrome manifested by a variety of CNS symptoms such as severe agitation with confusion, visual and auditory hallucinations, and a fear of impending death (Hoigne's syndrome), has been reported after administration of penicillin G procaine and, less commonly, after injection of the combination of penicillin G benzathine and penicillin G procaine. Other symptoms associated with this syndrome, such as psychosis, seizures, dizziness, tinnitus, cyanosis, palpitations, tachycardia, and/or abnormal perception in taste, also may occur.

Respiratory: Hypoxia; apnea; dyspnea.

Skin: Diaphoresis.

Special Senses: Blurred vision; blindness.

Urogenital: Neurogenic bladder; hematuria; proteinuria; renal failure; impotence; priapism.

OVERDOSAGE

Penicillin in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures.

DOSAGE AND ADMINISTRATION

Streptococcal (Group A) Upper Respiratory Infections (for example, pharyngitis)

Adults—a single injection of 1,200,000 units; older pediatric patients—a single injection of 900,000 units; infants and pediatric patients under 60 lbs.—300,000 to 600,000 units.

Syphilis

Primary, secondary, and latent—2,400,000 units (1 dose). Late (tertiary and neurosyphilis)—2,400,000 units at 7-day intervals for three doses.

Congenital—under 2 years of age: 50,000 units/kg/body weight; ages 2 to 12 years: adjust dosage based on adult dosage schedule.

Yaws, Bejel, and Pinta—1,200,000 units (1 injection).

Prophylaxis—for rheumatic fever and glomerulonephritis.

Following an acute attack, penicillin G benzathine (parenteral) may be given in doses of 1,200,000 units once a month or 600,000 units every 2 weeks.

METHOD OF ADMINISTRATION

BICILLIN L-A IS INTENDED FOR INTRAMUSCULAR INJECTION ONLY. DO NOT INJECT INTO OR NEAR AN ARTERY OR NERVE, OR INTRAVENOUSLY OR ADMIX WITH OTHER INTRAVENOUS SOLUTIONS. (SEE WARNINGS SECTION.)

Administer by DEEP INTRAMUSCULAR INJECTION in the upper, outer quadrant of the buttock. In neonates, infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

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

HOW SUPPLIED

Bicillin L-A (penicillin G benzathine injectable suspension) is supplied in packages of 10 disposable syringes as follows:

1 mL size, containing 600,000 units per syringe, (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 60793-700-10.

2 mL size, containing 1,200,000 units per syringe, (21 gauge, thin-wall 1-1/2 inch needle), NDC 60793-701-10.

4 mL size, containing 2,400,000 units per syringe (18 gauge x 1–1/2 inch needle), NDC 60793-702-10.

Store in a refrigerator, 2° to 8°C (36° to 46°F).

Keep from freezing.

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