

**Bicillin® L-A**

(penicillin G benzathine injectable suspension)

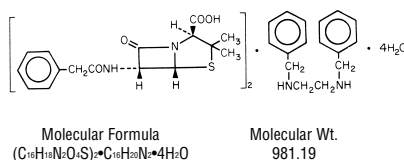
**Disposable Syringe**

for deep IM injection only

**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.**

**Rx only****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 4 mL size containing the equivalent of 2,400,000 units 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**

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 mucopolysaccharide. It is not active against the penicillinase-producing bacteria, which include many

strains of staphylococci.

The following *in vitro* data are available, but their clinical significance is unknown. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (Groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to penicillin G are *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Bacillus anthracis*, Clostridia species, *Actinomyces bovis*, *Streptobacillus moniliformis*, *Listeria monocytogenes*, and *Leptospira* species. *Treponema pallidum* is extremely susceptible to the bactericidal action of penicillin G.

**Susceptibility Test:** If the Kirby-Bauer method of disc susceptibility is used, a 20-unit penicillin disc should give a zone greater than 28 mm when tested against a penicillin-susceptible bacterial strain.

**INDICATIONS AND USAGE**

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.

**Veneral 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**

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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.**

**Pseudomembranous Colitis**

**Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, 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**

**any antibacterial agent.**

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 one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate 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 antibacterial drug clinically effective against *C. difficile* colitis.

**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.<sup>1,9</sup> (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**

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 over-growth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

**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 ade-

quate 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.)

#### 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; vasodilatation; 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.

The disposable syringe for this product incorporates several features that are designed to facilitate its use.

A single, small indentation, or "dot," has been punched into the metal ring that surrounds the neck of the syringe near the base of the needle. It is important that this "dot" be placed in a position so that it can be easily visualized by the operator following the intramuscular insertion of the syringe needle.

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2 to 3 seconds, carefully observe the barrel of the syringe immediately proximal to the location of the "dot" for appearance of blood or any discoloration. Blood or "typical blood color" may not be seen if a blood vessel has been entered—only a mixture of blood and Bicillin L-A. The appearance of any discoloration is reason to withdraw the needle and discard the syringe. If it is elected to inject at another site, a new syringe should be used. If no blood or discoloration appears, inject the contents of the syringe slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if, especially in neonates, infants and young children, symptoms or signs occur suggesting onset of severe pain.

Some disposable syringes may contain a small air bubble which should be disregarded since it does not affect administration of this product. DO NOT clear any air bubbles from the disposable syringe or needle as this may interfere with the visualization of any blood or discoloration during aspiration.

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:

4 mL size, containing 2,400,000 units per syringe (18 gauge x 2 inch needle), NDC 61570-148-10.

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

Keep from freezing.

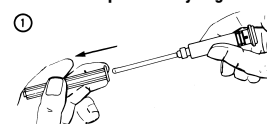
#### Also Available:

Bicillin L-A (penicillin G benzathine injectable suspension) is also available in packages of 10 TUBEX® Sterile Cartridge-Needle Units as follows:

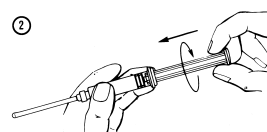
1 mL size, containing 600,000 units per TUBEX® (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 61570-146-10.

2 mL size, containing 1,200,000 units per TUBEX® (21 gauge, thin-wall 1-1/4 inch needle), NDC 61570-147-10.

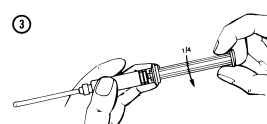
#### Directions for Use of Disposable Syringes



Detach ribbed plastic cylinder from needle hub and remove from needle cover.



The plastic cylinder now serves as a plunger rod. To engage, place self-threading narrow end of plunger rod against metal bushing protruding from the stopper of the syringe barrel and exert gentle inward pressure while turning clockwise.



Twist plunger rod clockwise until threads are locked, then release one-quarter turn. Sterility may be assured by not removing the needle cover until ready to make the injection.

#### REFERENCES

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3. DARBY, C. et al: Ischemia following an intragluteal injection of benzathine-procaine penicillin G mixture in a one-year-old boy. *Clin. Pediatrics*, 12:485, 1973.
4. BROWN, L. & NELSON, A.: Postinfectious intravascular thrombosis with gangrene. *Arch. Surg.*, 94:652, 1967.
5. BORENSTINE, J.: Transverse myelitis and penicillin (Correspondence). *Am. J. Dis. Child.*, 112:166, 1966.
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9. SCHANZER, H. et al: Accidental intra-arterial injection of penicillin G. *JAMA*, 242:1289, 1979.

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