CORRECTED PRESCRIBING INFORMATION
November 30, 2004

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:

R 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 dibenzylichlydramine with two molecules of penicillin G. It is chemically designated as (2S, 5R,6R)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azacycloc[3.2.0]heptane-2-carboxylic acid compound with N,N'-dibenzylpiperazinediamine (2:1), tetracydrate. 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:

Molecular Formula: C41H38N6O10Se
Molecular Weight: 981.19

Bicillin L-A contains penicillin G benzathine in aqueous suspension with sodium citrate buffer and, as w/v, approximate-ly 0.5% lecithin, 0.6% carbomethoxymethylcellulose, 0.6% povi-done, 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 0.3 to 0.5 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, 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. Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in wide-ly 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 small children, prompt consultation with an appropriate specialist is indicated if any evidence of compro mise of the blood supply occurs at, proximal to, or distal to the site of injection.2 (See PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections.)

Microbiology
Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplications. It acts through the inhibition of biosynthesis of cell-wall mucopeptide. 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 sig-nificance 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. Trenopena pallidum is extremely suscep-tible to the bactericidal action of penicillin G.

Susceptibility Test: If the Kirby-Bauer method of disc sus cetibility 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 microor ganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (includ ing sensitivity tests) and by clinical response. The following infections will usually respond to adequate dosages of intramuscular penicillin G benzathine:

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

General 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 indica tions listed in this insert.

Anaphylaxis
SERIOUS AND OCCASIONAL FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENCILLIN 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, 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 INSTI TUTED. ANAPHYLAXIS HAS BEEN ASSOCIATED WITH CARDI ORESPIRATORY ARREST AND DEATH. SHOULD THE DRUG 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 bacteria which are normally inhibited by its presence. C. 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 intravenous administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Bicillin L-A and other penicillin prepa rations has resulted in severe neurovascular damage, includ ing 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 fol lowing 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 blod formation; severe edema requiring anterior and/or posterior compart ment fasciectomy 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 compro mise of the blood supply occurs at, proximal to, or distal to the site of injection.2 (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 cardiorenal hyper sensitivity and/or drug-related 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 his tories 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 neuromuscular damage. (See WARNINGS, and DOSAGE AND ADMINISTRATION sections.)

Prolonged use of antibiotics may promote the over-growth of nonsusceptible organisms, including fungi. Should super-infection 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-
Nervousness; tremors; dizziness; somnolence; weakness; malaise; anorexia; nausea; vomiting;
Blurred vision; blindness.
Nephropathy.
Elevated BUN, creatinine, and SGOT.
Injection site reactions including pain, inflammation, local reaction;
Neurogenic bladder; hematuria; proteinuria; renal failure.
Serious anaphylactic reactions require immediate emergency treatment
with parenteral administration of penicillin G benzathine:
As with other penicillins, untoward reactions of the sensitivi-
threatening and amenable only to therapy with penicillin G. Serious
serious reactions may be controlled with antihistamines and, if
Gastrointestinal: Pseudoemembranous colitis. Onset of pseudoemembranous colitis symptoms may occur during or
after antibacterial treatment. (See WARNINGS section.)
Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.
The following adverse events have been temporally associat-
Adverse reactions and therapeutic effects of penicillin G benzathine
Cardiovascular: Cardio arrest; hypotension; tachycardia; palpitations; pulmonary hypertension; pulmonary embolism;
vasoconstriction; vasovagal reaction; cerebrovascular acci-
dent; syncope.
Gastrointestinal: Nausea, vomiting; blood in stool; intestinal necrosis.
Hemic and Lymphatic: Lymphadenopathy.
Injection Site. Injection site reactions including pain, inflam-
mation, lump, abscess, necrosis, edema, hemorrhage, cel-
lulitis, hypersensitivity, atrophy, ecchymosis, and skin ulcer.
Neurovascular reactions including warmth, vasospasm, palsy,
Nervous System: Nervousness; tremors; dizziness; somno-
lence; confusion; anxiety; euphoria; transfusion myelitis; seizures;
Musculoskeletal: Joint disorder; periostitis; exacerbation of arthritis; myoglobinuria; rhabdomyolysis.
Nervous System: Nervousness; tremors; dizziness; somnolence; confusion; anxiety; euphoria; transfusion myelitis; seizures; convulsions. 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, may also occur.
Respiratory: Hypoxia; apraxia; 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 neuromus-
cular hyper irritability or convulsive seizures.
DOSEAGE AND ADMINISTRATION
Streptococcal (Group A) Upper Respiratory Infections (for example, pharyngitis)
Adults—a single injection of 1,200,000 units; older patients—a single injection of 900,000 units; infants and pediatric patients under 60 lbs., 300,000 to 600,000 units.
Syphils Primary, secondary, and latent—2,400,000 units (1 dose). Late (tertiary and neurosyphils)—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 a severe 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 INJEC-
TION 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 injec-
tion 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 sec-
onds, 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
TUBEX
DOSAGE AND ADMINISTRATION

Full Text