June 11, 2024

Laboratórios Atral, S.A.
Rua da Estação, 1 e 1A
2600-726 Castanheira Ribatejo
Portugal
https://www.atral.pt/en/

IMPORTANT PRESCRIBING INFORMATION

Subject:

Temporary Importation of Lentocilin©, (Benzathine Benzylpenicillin Tetrahydrate) Powder and diluent for suspension for injection, 1,200,000 units with Foreign, non-U.S. Labeling to Address Supply Shortage

Dear Healthcare Provider,

To address the shortages of Bicillin® L-A (penicillin G benzathine injectable suspension) in the United States, Mark Cuban Cost Plus Drug Company, PBC ("MCCPDC") is coordinating with the U.S. Food and Drug Administration (FDA) to temporarily import Lentocilin© (Benzathine Benzylpenicillin Tetrahydrate) Powder and diluent for suspension for injection, 1,200,000 units into the United States. Benzathine benzylpenicillin is another name for Penicillin G benzathine.

Lentocilin©, (Benzathine Benzylpenicillin Tetrahydrate) Powder and diluent for suspension for injection 1,200,000 units, manufactured and marketed in Portugal by Laboratórios Atral S.A., is not FDA-approved.

Effective immediately, MCCPDC will distribute the following presentations of Lentocilin©, (Benzathine Benzylpenicillin Tetrahydrate) Powder and diluent for suspension for injection 1,200,000 units to address the shortage:

Product Description	Strength	Pack Size	NDC #	Batch #	Expiration Date
LENTOCILIN S 1200 1,200,000 units/4ML	1,200,000 units/4 ml	1 unit	84383-110	V055V007497V	03/31/2028

The barcode on the imported product label may not register accurately on the U.S. scanning systems. Institutions should manually input the imported product information into their systems and confirm that the barcode, if scanned, provides correct information. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

In addition, the packaging of the imported product does include serialization information. Lab Atral does not meet the Drug Supply Chain Security Act (DSCSA) requirements for the Interoperable Exchange of Information for Tracing of Human, Finished Prescription Drugs. However, the company is not registered in the GS1 system in US, thus the tracking function is not available.

There are key differences between the FDA approved Bicillin® L-A and Lentocilin©

- Lentocilin© labeling does not have a boxed warning. Please refer to the Bicillin L-A boxed warning.
- Lentocilin© carton labeling does not have the warning "Fatal if given by other routes". However, Lentocilin's product information states that "Lentocilin S Suspension for injection must be administered EXCLUSIVELY by DEEP INTRAMUSCULAR (IM) injection.".
- Lentocilin© contains soy phospholipids and may cause hypersensitivity reactions (urticaria, anaphylactic shock) in patients with a history of allergy to soybeans.
- Lentocilin© is supplied as powder for reconstitution compared to prefilled disposable syringes for Bicillin L-A. Follow instructions for the preparation of an intramuscular injection of Lentocilin® in the Preparation section below.
- **The volume of Lentocilin© 1,200,000 units after reconstitution is around 4 mL compared to 2 mL for Bicillin L-A 1,200,000 units.**
- Lentocilin© labeling includes detailed instructions for deep intramuscular administration in the Warnings section below:
    - Administer Lentocilin S suspension EXCLUSIVELY by DEEP INTRAMUSCULAR INJECTION in the external upper quadrant of the buttock.
    - In children and infants, the IM injections should be done, preferably, in the middle of the external lateral side of the thigh.
    - In infants younger than 2 years, and if considered necessary, the dosage may be divided and administered in two separate sites.
    - The IM injection site should be changed in case of repeated doses.
- Lentocilin© should be stored below 25ºC, in the original package to protect from light and moisture. Following reconstitution, benzylpenicillin benzathine should be used immediately.
- Lentocilin© will be available only by prescription in the U.S. However, the imported product does not have the statement "Rx only" on the labeling. An equivalent expression is included in carton box (Medicinal product subject to medical prescription).

Reporting Adverse Events:

Healthcare providers should report adverse events associated with the use of Lab Atral's Lentocilin© to MCCPDC by phone: 682-428-8081; email: dtc_quality@costplusdrugs.com. Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax:

- Complete and submit the report Online: www.fda.gov/medwatch/report.htm
- Regular Mail or Fax: Download form https://www.accessdata.fda.gov/scripts/medwatch/index.cfm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form or submit by fax to 1-800-FDA-0178 (1-800-332-0178).

Please ensure that your staff and others in your institution who may be involved in the administration of Lab Atral's Lentocilin© receive a copy of this letter and review the information.

To place an order, please contact TopRx at support@toprx.com or 1-800-542-8677.

This letter is not intended as a complete description of the benefits and risks related to the use of Lab Atral's Lentocilin©. Please refer to the enclosed full prescribing information.

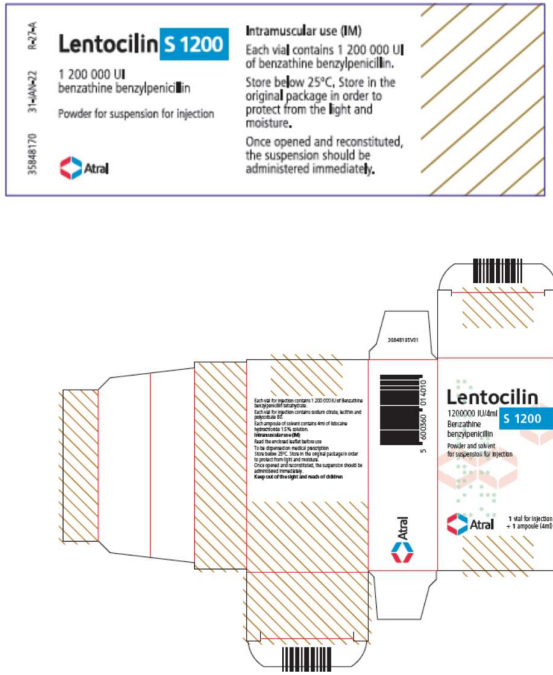
For additional information, please contact Mark Cuban Cost Plus Drug Company, PBC. at 682-428-8081; email: dtc_quality@costplusdrugs.com.

Sincerely,

Assinado por: **Augusto Eduardo Vieira Borges de Oliveira**
Num. de Identificação: 08662640
Data: 2024.06.11 15:48:14+01'00'

Eduardo Oliveira
Regulatory Affairs Director

Side-by-Side Product Comparison of Bicillin L-A and Lentocilin©

	US Product	Imported Product
Product Name	**Bicillin L-A**	**Lentocilin S 1200**
Dosage Form	**injectable suspension**	**Powder and diluent for suspension for injection**
Label		

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Matrícula na Conservatória do Registo Comercial de Vila Franca de Xira /NIPC: 500162085, Capital Social: 2.717.100,00 Euros

	US Product	Imported Product
Composition	Bicillin L-A contains penicillin G benzathine in aqueous suspension with sodium citrate buffer and, as w/v, approximately 0.65% sodium citrate, 0.59% povidone, 0.54% carboxymethylcellulose sodium, 0.53% lecithin, 0.12% methylparaben, and 0.013% propylparaben. Bicillin L-A contains approximately 0.11 mEq of sodium per 600,000 units of penicillin G (approximately 2.59 mg of sodium per 600,000 units of penicillin G).	**Vial – Powder for suspension for injection:** • Benzylpenicillin benzathine tetrahydrate – 1,200,000 units • Sodium citrate - 37 mg • Lecithin (0.5-1.5% used in Benzathine benzylpenicillin)- N.D. • Polysorbate 80 (0.1-0.3%used in Benzathine benzylpenicillin)- N.D. **Diluent for Parental use:** • Lidocaine hydrochloride monohydrate - 60 mg • Water for injections - 4 ml
	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 (actual volume of 1.17 mL contains 620,100), 1,200,000 (actual volume of 2.34 mL contains 1,240,200), and 2,400,000 (actual volume of 4.67 mL contains 2,475,100) units respectively of penicillin G as the benzathine salt.	
Indications	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.	Lentocilin S is indicated for the treatment of the following infections in adults and children: - Upper respiratory tract infections, namely group A streptococcal infections - Primary and secondary syphilis - Latent syphilis - Tertiary syphilis (in adults) - Congenital syphilis (in children) - Yaws - Bejel - Pinta Lentocilin S is also indicated prophylactically in the following situations: - Rheumatic fever - Diphtheria (including elimination of the asymptomatic carrier state) Consideration should be given to official guidelines for appropriate use of antimicrobial agents.

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Contraindications	A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.	Hypersensitivity to the active substance, to other penicillin or to any of the excipients. Hypersensitivity to lidocaine or local anesthetics of the amide type.
Precautions	PRECAUTIONS: 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.	Before initiating therapy with benzylpenicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillin, cephalosporins, and other beta-lactam antibiotics. Contact with the penicillin during handling the product should be avoided due to the possibility of skin sensitization. To minimize the overgrowth of resistant bacteria and maintain the effectiveness of benzylpenicillin, this medicine should only be used in the treatment of infections proven to be caused by susceptible bacteria. Therapy should be based on bacteriological studies (including sensitivity tests) and the patient's clinical response. Prolonged administration of Lentocilin S can occasionally result in overgrowth of non-susceptible organisms particularly Candida, Pseudomonas or Enterobacter. Antibiotic treatment modifies the commensal flora of the colon, allowing the growth of Clostridium difficile. This microorganism produces toxins, which are responsible for diarrhea associated to antibiotherapy, which can range from mild diarrhea to fatal colitis. Patients with diarrhea during or even up to two months after treatment with antibiotics should be subject to investigation and differential diagnosis. Confirming pseudomembranous colitis, treatment should be discontinued and, if necessary, use supportive hydro-electrolyte measures, recommended antibiotherapy and protein supplement. Because of the risk of neurotoxicity, caution is recommended especially in the case of administration of high doses of benzylpenicillin to renal impaired patients. During prolonged treatment with high doses of benzylpenicillin is recommended to monitor the renal and haematological functions. The use of benzylpenicillin for more than 2 weeks may be associated with an increased risk of neutropenia and incidence of

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		immune complex self-limited sickness-like reactions. Special precautions should be taken in order to avoid intravenous and intraarterial administration or injection into or near major peripheral nerve or blood vessel, since such injections may produce severe and/or permanent neuromuscular damage. In case of evidence of impaired blood flow at the injection site - proximal or distal – an appropriate specialized physician should be immediately consulted. Special caution is recommended when treating patients with spirochetal infections, particularly syphilis, due to the possibility of a Jarisch - Herxheimer reaction. This is a very common reaction when benzylpenicillin is used to treat syphilis, occurring in 50% of patients with primary syphilis, 75% of those treated for secondary syphilis and 30% of those treated for neurosyphilis. This reaction usually occurs 2-12 hours after initiation of penicillin therapy and is characterized by the occurrence of headache, fever, chills, sweating, sore throat, myalgia, arthralgia, malaise, increased heart rate and an increase in blood pressure followed by its decrease. This reaction is probably caused by the release of endotoxins from the treponemes and should not be confused with a hypersensitivity reaction. The reaction may be dangerous in cardiovascular syphilis or when there is a serious risk of increased local lesions such as optic atrophy. It is recommended the use of oxidative enzymatic methods when testing glucose in urine during therapy with benzylpenicillin. False positive results can occur with the use of non-enzymatic methods. Benzylpenicillin may interfere with other diagnostic tests such as the Coombs test, tests for the determination of proteins in plasma and urine and the test for the determination of plasmatic uric acid (copper-chelate method). Due to the lidocaine content (present in the ampoule), Lentocilin S should be used with caution in the following situations: - presence of cardiovascular, hepatic or renal dysfunction, inflammation and/or infection at the injection site or sensitivity to local anesthetics of the amide type,

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		- children, the elderly and patients with acute illnesses or debilitated, - patients on concomitant CNS depressant drugs.
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.	Bacteriostatic antibiotics: Bacteriostatic antibiotics, such as tetracycline, erythromycin and chloramphenicol, may antagonize the bactericidal effect of benzylpenicillin by interfering with active bacterial growth necessary to benzylpenicillin's effect. Oral contraceptives: The efficacy of oral contraceptives may be impaired in case of concomitant therapy with benzylpenicillin, which may result in an unwanted pregnancy. Women taking oral contraceptives should be alerted to this situation and should be informed about the need to adopt alternative methods of contraception. Methotrexate: Penicillins may reduce the renal excretion of methotrexate causing a potential increase in its toxicity. Probenecid: Probenecid decreases the renal tubular secretion of benzylpenicillin. Its concomitant use with benzylpenicillin can prolong blood levels of benzylpenicillin. Probenecid may be used therapeutically for this purpose.
Warnings	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. Anaphylaxis SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE	Lentocilin S suspension for injection should ONLY be administered by INTRAMUSCULAR ROUTE. To avoid injury, Lentocilin S suspension should not be administered by intravenous, intraarterial or subcutaneous route, in the adipose layer, into or near a peripheral nerve or blood vessel. Before injecting the suspension, the position of the needle should be controlled by aspiration. If blood shows up in the syringe, pull back the needle and inject on another site. Administer Lentocilin S suspension EXCLUSIVELY by DEEP INTRAMUSCULAR INJECTION in the external upper quadrant of the buttock. In children and infants, the IM injections should be done, preferably, in the middle of the external lateral side of the thigh. In infants younger than 2 years, and if considered necessary, the dosage may

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	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. Severe cutaneous adverse reactions Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in patients taking penicillin G (the active moiety in Bicillin L-A). When SCAR is suspected, Bicillin L-A should be discontinued immediately and an alternative treatment should be considered. Clostridioides difficile Associated Diarrhea Clostridioides 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.	be divided and administered in two separate sites. The IM injection site should be changed in case of repeated doses. Deep IM administration of this medicine requires a rigorous technique and should be performed only by experienced health technicians and in places prepared for the emergency treatment of a possible anaphylactic reaction. **A needle to use in the administration of the injectable suspensions should have a minimum internal diameter of 0.8 mm (caliber: 18 gauge).** **The deep IM injection should be made slowly and with a constant flow rate to prevent needle blockage. If the needle is clogged, replace it with a new needle.** The deep IM injection should be discontinued if there are signs or symptoms of immediate acute pain, especially in children and infants. Serious hypersensitivity reactions (anaphylactic reactions), sometimes fatal, have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, therapy with Lentocillin S should be discontinued immediately and the appropriate therapy instituted. In case of severe anaphylactic reaction, immediate emergency treatment (including adrenaline, corticosteroids, airway management, oxygen) is required. Usually, subcutaneous, or intravenous adrenaline is the treatment of choice for an immediate or accelerated hypersensitivity reaction to a penicillin.

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	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. See administration instructions below. 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 consistent with the diagnosis of Nicolau syndrome. 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	

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	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.) FOR DEEP INTRAMUSCULAR INJECTION ONLY. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. Therefore, do not inject intravenously or admix with other intravenous solutions. (See DOSAGE AND ADMINISTRATION section.) Administer by DEEP INTRAMUSCULAR INJECTION ONLY in the upper, outer quadrant of the buttock (dorsogluteal) or the ventrogluteal site. Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh. Because of these adverse effects and the vascularity of this region, administration in the anterolateral thigh is not recommended.	
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	Lentocilin S suspension for injection is to be EXCLUSIVELY administered by DEEP INTRAMUSCULAR (IM) INJECTION. Deep IM administration of this medicine requires a rigorous technique and should be performed only by experienced health technicians and in places prepared for the emergency treatment of a possible anaphylactic reaction. Posology Adults Group A streptococcal infections - Upper respiratory tract infections: 1,200,000 units in a single dose. Primary, secondary and early latent syphilis: 2,400,000 units in a single dose (injection at two different sites). Late latent syphilis or of unknown duration: 2,400,000 units (injection at two different sites) weekly for 3 consecutive weeks. Tertiary syphilis: 2,400,000 units (injection at two different sites) weekly for 3 consecutive weeks.

	US Product	Imported Product
	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 (dorsogluteal) or the ventrogluteal site. In neonates, infants and small children, the midlateral aspect of the thigh may be preferable. Administration in the anterolateral thigh is not recommended due to the adverse effects observed (see WARNINGS section), and vascularity of this region. 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.	Yaws, bejel and pinta: 1,200,000 units in a single dose. Prophylaxis of rheumatic fever: 1,200,000 units every 4 weeks. In high-risk patients it is recommended administration every 3 weeks. Prevention of diphtheria, including elimination of the asymptomatic carrier state: 1,200,000 units in a single dose. Newborns aged ≥ 1 month Asymptomatic congenital syphilis: 50,000 units/kg in a single dose (maximum dose: 2,400,000 units/dose). Benzathine benzylpenicillin is not recommended in newborns with proven or highly probable congenital syphilis. Children Group A Streptococcal infections - Upper respiratory tract infections: 25,000 - 50,000 units/kg in a single dose (maximum dose: 1,200,000 units/dose) or weight < 27 kg: 300,000-600,000 units in a single dose weight ≥ 27 kg: 1,200,000 units in a single dose. - Primary, secondary and early latent syphilis: 50,000 units/kg (maximum dose: 2,400,000 units/dose) in a single dose. - Late latent syphilis or latent syphilis of unknown duration: 50,000 units/kg (maximum dose: 2,400,000 units/dose) weekly for 3 weeks. - Yaws, bejel and pinta: 300,000 units as a single dose in children aged less than 6 years or 1,200,000 units in a single dose in children aged 6 years and older. -Prophylaxis of rheumatic fever: 25,000 - 50,000 units/kg in a single dose (maximum dose: 1,200,000 units/dose) or weight < 27 kg: 300,000 - 600,000 units in a single dose

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		weight ≥ 27 kg: 1,200,000 units in a single dose. Prevention of diphtheria (including elimination of the asymptomatic carrier state): - children aged < 6 years (or weight < 30 kg): 600,000 units in a single dose - children aged ≥ 6 years (or weight ≥ 30 kg): 1,200,000 units in a single dose. Special populations Elderly - Dose adjustment is not necessary. However, since the elderly have a higher likelihood of decreased renal function, this must be taken into consideration during the selection of the posology and may be useful to monitor renal function. Renal insufficiency - Toxic concentrations of benzylpenicillin following administration of the usually recommended dose are not expected. Liver insufficiency - Dose adjustment is not necessary.
Preparation		**Follow carefully the next instructions, to ensure obtaining a homogeneous suspension before intramuscular administration.** The diluent is provided as 4ml of 1.5% lidocaine hydrochloride solution contained in an amber Type I glass ampoule. The deep IM administration of this medicine requires a rigorous technique and should only be performed by experienced health technicians and in places prepared for the emergency treatment of a possible anaphylactic reaction. The needle to use in the administration of the injectable suspensions should have a minimum internal diameter of 0.8 mm (caliber: 18 gauge).

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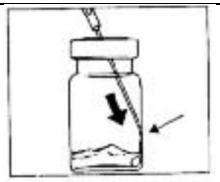
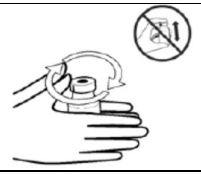
		 Disinfect the rubber stopper of the vial with alcohol and insert the needle through its center.  Without touching the powder deposited on the bottom, carefully inject the liquid of the ampoule in the vial, making it slide through the inside face of the same. Do not inject the liquid directly into the powder. Remove the needle from the vial.  Homogenize the suspension by rotating the vial tightly between the hands for about 20 seconds. The final concentration of suspension for injection prepared as per the above procedure is 1,200,000 units/4 ml. The final volume of suspension for injection is approximately 4 mL After preparation and complete homogenization of the suspension in the vial, transfer it immediately to the syringe and proceed to its administration as soon as possible. Whenever possible use a recently prepared suspension. The deep IM injection should be made slowly and with a constant flow rate to prevent needle blockage and should be discontinued if there are signs or symptoms of immediate acute pain, especially in children and infants. If the needle is clogged, replace it with a new needle (internal diameter greater than 0.8 mm, i.e. 18 gauge).
Overdosage	Penicillin in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures.	Cases of overdose have not been described. However, the penicillins have the potential to cause neuromuscular hyperirritability or seizures.

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		In case of overdose a doctor should be contacted immediately. Since there is no antidote, treatment must be symptomatic and supportive. Benzylpenicillin is removed by dialysis.
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 adverse reactions have been reported with Bicillin L-A during post-marketing experience: Skin and Appendages: Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS). (See WARNINGS) The following have been reported with parenteral penicillin G (the active moiety in Bicillin L-A): 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: severe cutaneous adverse reactions (SCAR), such as toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP). (See WARNINGS.) 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	The most common undesirable effects of benzylpenicillin are hypersensitivity reactions, especially skin rashes. Anaphylactic reactions occurred occasionally, which have sometimes been fatal. The overall incidence of allergic reactions to penicillin ranges between 1 and 10%. Anaphylactic reactions occur in approximately 0.05% of patients, usually after parenteral administration. The following undesirable effects were observed with benzylpenicillin: Blood and lymphatic system disorders - Eosinophilia and hemolytic anemia (both with immunological basis), leukopenia and thrombocytopenia. These effects are usually reversible after discontinuation of treatment. Immune system disorders - Hypersensitivity reactions to penicillin cause a wide variety of clinical syndromes. Immediate reactions include anaphylaxis, laryngeal edema, angioedema, urticaria and maculopapular rashes. Late reactions include hemolytic anemia and immune complex self-limited sickness-like reactions, characterized by fever, malaise, urticaria, arthralgia, myalgia, lymphadenopathy and splenomegaly. In order to determine which patients will probably develop severe allergic reactions, hypersensitivity skin tests may be used. Jarisch – Herxheimer reaction. Nervous system disorders - Benzylpenicillin is very irritating to the central and peripheral nervous systems. Neurotoxic reactions include anxiety, asthenia, cerebrovascular accident (CVA), confusion, dizziness, euphoria, nervousness, hallucinations, headache, neuropathy, neurovascular injury, localized or generalized seizures, coma, tremor and vasospasm at the administration site, and occur after parenteral administration of benzylpenicillin potassium. These reactions are most common when the benzylpenicillin is given daily in doses of more than 20,000,000 IU intravenously to renal impaired patients.

	US Product	Imported Product
	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 (a component of Bicillin L-A): Body as a Whole: Hypersensitivity reactions including allergic vasculitis, pruritus, fatigue, asthenia, and pain; aggravation of existing disorder; headache, Nicolau syndrome. 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,	The accidental injection of preparations of benzylpenicillin into or near the nerves may produce neuromuscular damage, which rarely may be permanent. Rarely, inadvertent intravascular administration of benzathine benzylpenicillin or procaine benzylpenicillin, including direct administration into an artery - or adjacent to an artery - causes occlusion, thrombosis and severe neurovascular injury, especially in children. Deep injection in the gluteal muscles can cause paralysis, dysfunction and painful irritation of the sciatic nerve. Repeated intramuscular injection of benzylpenicillin preparations in the anterolateral side of the thigh of newborns has rarely caused generalized muscular contractions, as well as atrophy and fibrosis of the quadriceps femoris muscle. After intramuscular administration of benzathine benzylpenicillin Hoigné syndrome may occur, characterized by agitation accompanied by symptoms such as fear of impending death and visual and auditory hallucinations. Transversal myelitis with permanent paralysis, gangrene requiring amputation of fingers and the more proximal regions of the extremities, and necrosis with formation of scars surrounding the site of injection, have occurred after injections in the buttocks, thighs and deltoid muscle. Eye disorders - Blurred vision, transient blindness. Cardiac disorders - Hypotension, palpitations, syncope, tachycardia, vasodilation and vasovagal syndrome characterized by anxiety, sweating, hypotension, peripheral arterial vasodilation and bradycardia. Cardiopulmonary arrest and death due to inadvertent IV administration. Respiratory, thoracic and mediastinal disorders - Apnea, dyspnea, hypoxia, pulmonary embolism and pulmonary hypertension. Gastro-intestinal disorders - Intestinal necrosis, melena, nausea, vomiting, and pseudomembranous colitis, which can arise during or after treatment.

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	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.	Hepatobiliary disorders - Transient increases in SGOT, hepatitis and cholestatic jaundice. Skin and subcutaneous tissue disorders - Diaphoresis, pruritus and urticaria. Musculo-skeletal, connective tissue and bone disorders - Arthritis, arthropathy, myoglobinuria, periostitis and rhabdomyolysis. Renal and urinary disorders - Hematuria, neurogenic bladder, renal impairment, proteinuria and increased serum BUN and creatinine. Reproductive system and breast disorders - Impotence and priapism General disorders and administration site conditions - Parenteral administration of benzylpenicillin preparations may cause dose-related injection site reactions and are the result of a direct toxic effect of the drug. IM administration of high doses of benzylpenicillin benzathine (in particular more than 600,000 IU of benzylpenicillin) in a single injection site can result in painful tumefaction and endothelial injury on site. IM administration of benzylpenicillin has been associated with the occurrence of the following side effects at the administration site: inflammation, pain, abscess, edema, hemorrhage, cellulitis, atrophy and cutaneous ulceration. It has also been reported cases of fever and fatigue associated with the use of benzylpenicillin.
Usage in pregnancy	Safe use in pregnancy and lactation has not been established; therefore, use in pregnant women, nursing mothers or women who may become pregnant requires that possible benefits be weighed against possible hazards to mother and child.	The safe use of benzylpenicillin during pregnancy has not been clearly established. There are no adequate and controlled studies on the use of benzylpenicillin during pregnancy. Human experience with penicillins during pregnancy has not shown any effect on fertility or fetal harm when mice, rats and rabbits were exposed to benzylpenicillin. As with all medicines, use of Lentocilin S during pregnancy should be avoided unless the physician considers its prescription essential.

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Storage Conditions	Store in a refrigerator, 2° to 8°C (36° to 46°F). Keep from freezing.	Store below 25ºC. Store in the original package to protect from light and moisture. Following reconstitution, benzylpenicillin benzathine should be used immediately.
How Supplied	2 mL size, containing 1,200,000 units per syringe, (21 gauge, thin-wall 1-1/2-inch needle), with 0.22 mEq of sodium per 1,200,000 units of penicillin G (5.17 mg of sodium per 1,200,000 units of penicillin G), NDC 60793-701-10. 4 mL size, containing 2,400,000 units per syringe (18 gauge, × 1–1/2-inch needle), with 0.45 mEq of sodium per 2,400,000 units of penicillin G (10.32 mg of sodium per 2,400,000 units of penicillin G), NDC 60793-702-10.	1 vial and 1 amber glass ampoule of diluent for reconstitution