For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

BENZATHINE PENICILLIN INJECTION I.P.

Penidure® LA

LONG-ACTING (Single Dose Vial)

1. GENERIC NAME

Benzathine Penicillin Injection I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Penidure LA 6: Each vial contains Benzathine Penicillin I.P. 6,00,000 units
Reconstituted suspension (approx. 2 ml) contains approx. 0.13% w/v Methyl Paraben IP and 0.015% w/v Propyl Paraben IP as preservatives.

Penidure LA 12: Each vial contains Benzathine Penicillin I.P. 12,00,000 units
Reconstituted suspension (approx. 4 ml) contains approx. 0.13% w/v Methyl Paraben IP and 0.015% w/v Propyl Paraben IP as preservatives.

List of Excipients

Penidure LA 6: Methyl Paraben I.P., Propyl Paraben I.P., Sodium Citrate U.S.P. Anhydrous, Sodium Carboxymethyl Cellulose I.P., Polyvinylpyrrolidone I.P.

Penidure LA 12: Methyl Paraben I.P., Propyl Paraben I.P., Sodium Citrate U.S.P. Anhydrous, Sodium Carboxymethyl Cellulose I.P., Polyvinylpyrrolidone I.P.

Sodium Citrate U.S.P. Anhydrous, Sodium Carboxymethyl Cellulose I.P., Polyvinylpyrrolidone I.P. are used as Buffering and suspending agents.

All strengths/presentations mentioned in this document might not be available in the market.

3. DOSAGE FORM AND STRENGTH

Dosage Form: Sterile Powder for Reconstitution as Aqueous Suspension
For Strength: Refer Section 2.

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Licensed User – Pfizer Limited, India

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

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 Benzathine Penicillin:

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

Venereal Infections- Syphilis, yaws, bejel, pinta.

Medical conditions in which Benzathine Penicillin Therapy is indicated as Prophylaxis:

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

4.2 Posology and method of administration

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

Adults — a single injection of 12,00,000 units; older pediatric patients — a single injection of 9,00,000 units; infants and pediatric patients under 60 lbs.—.300,000 to 6,00,000 units.

Syphilis:

Primary, secondary, and latent — 24,00,000 units (1 dose). Late (tertiary and neurosyphilis) — 24,00,000 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: 12,00,000 units (1 injection)

Prophylaxis: for rheumatic fever and glomerulonephritis.
Following an acute attack, Benzathine Penicillin (parenteral) may be given in doses of 12,00,000 units once a month or 6,00,000 units every 2 weeks.

Method of Administration

Benzathine Penicillin 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE 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 discolouration prior to administration whenever solution and container permit.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 BENZATHINE PENICILLIN WHICH HAS BEEN ASSOCIATED WITH CARDIORESPIRATORY ARREST AND DEATH. Prior to administration of this drug, carefully read the SPECIAL WARNINGS AND PREACUTIONS FOR USE, UNDESIRABLE EFFETCS, and POSOLOGY AND METHOD OF ADMINISTRATION sections of the labeling.

Benzathine Penicillin 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 Benzathine Penicillin careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, Benzathine Penicillin 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 Benzathine Penicillin). When SCAR is suspected, Benzathine Penicillin 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 Benzathine Penicillin, 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. See administration instructions below.

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

Inadvertent intravascular administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Benzathine Penicillin 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 indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection. (See PRECAUTIONS, and POSOLOGY AND METHOD OF ADMINISTRATION sections.)

FOR DEEP INTRAMUSCULAR INJECTION ONLY. There have been reports of inadvertent intravenous administration of Benzathine Penicillin which has been associated with cardiorespiratory arrest and death. Therefore, do not inject intravenously or admix with other intravenous solutions. (See POSOLOGY AND METHOD OF 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.

PRECAUTIONS

General

Prescribing Benzathine Penicillin 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, and POSOLOGY AND METHOD OF ADMINISTRATION sections.)

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

Benzathine Penicillin contains approximately 0.11 mEq of sodium per 6,00,000 units of penicillin G (approximately 2.59 mg of sodium per 6,00,000 units of penicillin G).

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.

4.5 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.

4.6 Use in special populations

Pregnancy

Teratogenic effects: 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 reproductive 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 Benzathine Penicillin is administered to a nursing woman.

Pediatric Use

(See THERAPEUTIC INDICATIONS AND POSOLOGY AND METHOD OF ADMINISTRATION sections.)

Geriatric Use

Clinical studies of Benzathine Penicillin 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

PHARMACOKINETIC PROPERTIES) 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.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that benzathine penicillin may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

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 Benzathine Penicillin during post-marketing experience:

Skin and Appendages: Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS). (See SPECIAL WARNINGS AND PRECAUTIONS FOR USE.)

The following have been reported with parenteral penicillin G (the active moiety in Benzathine Penicillin):

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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). 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 Disorders: Pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (See SPECIAL WARNINGS AND PRECAUTIONS FOR USE section).

Hematologic Disorders: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurological Disorders: Neuropathy.

Urogenital Disorders: Nephropathy.

The following adverse events have been temporally associated with parenteral administration of Benzathine Penicillin (a component of Benzathine Penicillin):

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

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

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

Hemic and Lymphatic System: 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 System: Elevated BUN, creatinine, and SGOT.

Musculoskeletal System: 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 Benzathine Penicillin 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 System: Hypoxia; apnea; dyspnea.

Skin: Diaphoresis

Special Senses: Blurred vision; blindness.

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 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.

5.2. Pharmacodynamic properties

Microbiology:

It is not active against the penicillinase-producing bacteria, which include many strains of *staphylococci*. 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 sensitive to penicillin G are *Neisseria gonorrhoea, Corynebacterium diphtheria, Bacillus anthracis, Clostridia, Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes*, and *Leptospira.*
Treponema pallidum is extremely sensitive to the bactericidal action of Penicillin G.

Disc Susceptibility Tests:

Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure has been recommended for use with discs for testing susceptibility to ampicillin-class antibiotics. Interpretations correlate diameters of the disc test with MIC values for Amoxycillin. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g. Urine) in which high antibiotic levels are attained.

5.3 Pharmacokinetic properties

Absorption/ Distribution

Benzathine Penicillin has an extremely low solubility and thus 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 Benzathine Penicillin 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 12,00,000 units. Blood concentrations of 0.003 units per ml may still be detectable 4 weeks following administration of 12,00,000 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 the other tissues and the spinal fluid to a lesser degree.

Elimination

With normal kidney function, the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals when impaired kidney function, excretion is considerably delayed.

6. NONCLINICAL PROPERTIES

6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

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

7. DESCRIPTION

A white crystalline powder, almost odourless, visibly free from foreign particles.

8. PHARMACEUTICAL PARTICULARS

8.1. Incompatibilities

None

8.2. Shelf-life

24 months

8.3. Packaging information

A clear glass 7.5ml vial, USP Type III

8.4. Storage and handling instructions

Prior to reconstitution: Store below 25°C.

After reconstitution: Use immediately. If kept, use within 24 hours when stored below 25°C. Shake vial vigorously before withdrawing the dose. Discard any unused portion.

Instruction for Use/Handling

Penicillin sensitivity test required before administration of the product.

Keep out of reach of children.

Reconstitution:

Penidure LA 6 - Reconstitute by adding 1.5ml Sterile water for Injection I.P.
(Reconstituted suspension volume approx. 2ml)

Penidure LA 12 - Reconstitute by adding 3ml Sterile water for Injection I.P.
(Reconstituted suspension volume approx. 4ml)

9. PATIENT COUNSELLING INFORMATION

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 Benzathine Penicillin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Benzathine Penicillin 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 Benzathine Penicillin or other antibacterial drugs in the future.

10. DETAILS OF MANUFACTURER

M/s. Inject Care Parenenterals Pvt. Limited.,
Plot No. 130, Silvasa Road, GIDC, Vapi, 396 195, Dist.- Valsad, Gujarat, India

Marketed by

Pfizer Limited., The Capital-A wing, 1802,18th Floor, Plot No. C-70, G Block,
Bandra-Kurla Complex, Bandra (East), Mumbai-400 051, India

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Mfg. Lic. No. G/28/1216* permission dated 03 Mar 2023 (*License renewed/ retain every 5 years as per regulation)

12. DATE OF REVISION

January 2023