NEW ZEALAND DATA SHEET

1. PRODUCT NAME

BICILLIN L-A®
Benzathine Benzylpenicillin 1,200,000 Units/2.3 mL suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BICILLIN L-A contains benzathine benzylpenicillin (the benzathine salt of benzylpenicillin) in aqueous suspension

1,200,000 Units/2.3 mL pre-filled syringe, containing benzathine benzylpenicillin tetrahydrate 1016.6 mg/2.3 mL.

Excipient(s) with known effect

- Methyl hydroxybenzoate
- Propyl hydroxybenzoate.

BICILLIN L-A contains approximately 0.05 mEq of sodium per 600,000 units of benzylpenicillin (approximately 1.23 mg of sodium per 600,000 units of benzylpenicillin).

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Suspension for injection pre-filled syringe with needle.

BICILLIN L-A in the disposable pre-filled syringe formulation is a viscous and opaque white suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Intramuscular benzathine benzylpenicillin is indicated in the treatment of infections due to penicillin-sensitive micro-organisms 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 benzylpenicillin:

Streptococcal infections (Group A - without bacteraemia). Mild-to-moderate infections of the upper respiratory tract (e.g. pharyngitis).

Venereal infections - Syphilis, yaws, bejel and pinta.

Medical conditions in which benzathine benzylpenicillin therapy is indicated as prophylaxis:

Rheumatic fever and/or chorea - Prophylaxis with benzathine benzylpenicillin 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.

4.2 Dose and method of administration

Dose

Use a concentration of 442 mg/mL when measuring part doses. The quantity of benzathine benzylpenicillin is based on 1,200 Units/mg potency.

Streptococcal (Group A) upper respiratory infections (for example, pharyngitis)

A single injection of 1,200,000 Units for adults.

A single injection of 900,000 Units for older children.

A single injection of 300,000 to 600,000 Units for infants and for children under 27 kg.

Venereal infections

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

Congenital (with normal CSF) - under 2 years of age: 50,000 Units/kg body weight; ages 2-12 years; adjust dosage based on adult dosage schedule.

Yaws, bejel and pinta - 1,200,000 Units (single injection).

Prophylaxis - for rheumatic fever and glomerulonephritis

The dosing recommendation for benzathine penicillin G is 1,200,000 units for patients weighing ≥20 kg and 600,000 units for patients weighing <20 kg, every 4 weeks, except in patients considered to be at high risk, for whom 3 weekly administration is recommended.

Method of Administration

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.

Administer by DEEP, INTRAMUSCULAR INJECTION in the upper, outer quadrant of the buttock. In 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 section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), and vascularity of this region. When doses are repeated, vary the injection site.

Method of administration is the same as with conventional syringe. Remove needle cover by grasping it securely; twist and pull. Introduce needle into patient, aspirate by pulling back slightly on the plunger, and inject.

Discard any unused portion.

4.3 Contraindications

BICILLIN L-A is contraindicated in patients who have had previous experience of a major allergy or anaphylaxis to a cephalosporin or penicillin.

Hypersensitivity to any of the excipients.

4.4 Special warnings and precautions for use

Allergic Reactions

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of sensitivity to multiple allergens. There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins and other allergens. BICILLIN L-A should be given with caution to patients who have previously experienced signs and symptoms of allergy associated with a cephalosporin or penicillin. If an allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents, e.g. pressor amines, antihistamines and corticosteroids. Severe anaphylactoid reactions require emergency treatment with adrenaline. Oxygen and intravenous corticosteroids and airway management, including intubation, should also be administered as indicated.

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma. Whenever allergic reactions occur, penicillin should be withdrawn unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to penicillin therapy.

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 generalised exanthematous pustulosis (AGEP) have been reported in patients taking benzylpenicillin (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.

Administration Precautions

Do not inject intravenously or admix with other intravenous solutions. There have been

reports of inadvertent intravenous administration of benzathine which has been associated with cardiorespiratory arrest and death (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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 oedema requiring anterior and/or posterior compartment fasciotomy in the lower extremity.

Severe effects and complications following accidental intravascular administration 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 sections 4.3 CONTRAINDICATIONS and 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

Antibiotic-associated Pseudomembranous Colitis

Antibiotic-associated pseudomembranous colitis has been reported with many antibiotics including penicillin. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridiodes difficile*.

C. difficile produces toxins A and B which contribute to the development of *Clostridioides difficile* associated-diarrhea (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.

The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Non-susceptible Organisms and Superinfections

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

Streptococcal Infections

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.

Blood and Kidney Function Tests

In prolonged therapy with penicillin and particularly with high-dosage schedules, periodic evaluation of the renal and haematopoietic systems is recommended.

Fluids, electrolytes and protein replacement therapy should be provided when indicated.

Paediatric Use

See sections 4.1 THERAPEUTIC INDICATIONS and 4.2 DOSE AND METHOD OF ADMINISTRATION.

Geriatric Use

Clinical studies of benzylpenicillin 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 section 5.2 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.

Effects on Laboratory Tests

Penicillins may interfere with:
- Urinary glucose test
- Coomb's tests
- Tests for urinary or serum proteins
- Tests which use bacteria e.g. Guthrie test.

Penicillins can interfere with the copper sulphate reagent method of testing for glycosuria, resulting in falsely elevated or falsely decreased readings. Such interference does not occur with the glucose oxidase method.

Other

BICILLIN L-A contains approximately 0.11 mEq of sodium per 1,200,000 units of benzylpenicillin (approximately 2.46 mg of sodium per 1,200,000 units of benzylpenicillin).

4.5 Interaction with other medicines and other forms of interaction

Tetracycline may antagonise the bactericidal effect of penicillin and concurrent use of these drugs should be avoided.

The rate of excretion of the penicillins is decreased by concomitant administration of probenecid which prolongs, as well as increases, blood levels of the penicillins.

Penicillins may reduce the excretion of methotrexate thereby increasing the risk of methotrexate toxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy

Human experience with penicillins during pregnancy has not shown any 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. BICILLIN L-A should be used during pregnancy only if clearly needed.

Breast-feeding

Penicillin can be detected in breast milk with the potential for hypersensitivity reactions (e.g. drug rashes) or gastrointestinal disorders (e.g. diarrhoea or candidosis) in the breast-fed infant. Consequently, breastfeeding might have to be discontinued.

Fertility

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

4.7 Effects on ability to drive and use machines

During treatment with BICILLIN L-A undesirable effects may occur (e.g. allergic reactions, dizziness, seizures which may influence the ability to drive and use machines. Patients should be cautious when driving or operating 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.

The following adverse reactions have been reported with BICILLIN L-A during post-marketing experience:

Skin and Other Subcutaneous Tissue Disorders: Stevens-Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS) (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The following adverse reactions have been reported with parenteral benzylpenicillin (the active moiety in BICILLIN L-A):

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal oedema, fever, eosinophilia, other serum sickness-like reactions (including chills, fever, oedema, arthralgia and prostration), and anaphylactic/anaphylactoid reaction (including shock and death); severe cutaneous adverse reactions (SCAR), such as toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) (see section 4.4 Special warnings and precautions for use).

Fever and eosinophilia may frequently be the only reaction observed.

Gastrointestinal: Pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Haematologic: Haemolytic anaemia, leucopenia, thrombocytopenia

Neurologic: Neuropathy

Urogenital: Nephropathy, acute interstitial nephritis

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

The following adverse events have been temporally associated with parenteral administration of benzathine benzylpenicillin (the active moiety of BICILLIN L-A):

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

Haematological: Lymphadenopathy.

Injection Site: Injection site reactions including pain, inflammation, lump, abscess, necrosis, oedema, haemorrhage, 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 benzylpenicillin procaine and, less commonly, after injection of the combination of benzylpenicillin benzathine and benzylpenicillin 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, apnoea, dyspnoea.

Skin and Other Subcutaneous Tissue Disorders: Diaphoresis.

Special Senses: Blurred vision, blindness.

Urogenital: Neurogenic bladder, haematuria, proteinuria, renal failure, impotence, priapism.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Penicillin in overdosage has the potential to cause neuromuscular hyperirritability and convulsive seizures. This is particularly so if the penicillin is given to patients with renal failure.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Benzylpenicillin exerts a bactericidal action against penicillin-sensitive micro-organisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall peptidoglycan, rendering the cell wall osmotically unstable. It is not active against the penicillinase-producing bacteria or against organisms resistant to beta-lactams because of alterations in the penicillin-binding proteins.

The following *in-vitro* data are available but the clinical significance is unknown.

Benzylpenicillin 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 benzylpenicillin are: *Neisseria gonorrhoea*, *Corynebacterium diphtheria*, *Bacillus anthracis*, Clostridia spp, *Actinomyces bovis*, *Streptobacillus moniliformis*, *Listeria monocytogenes* and Leptospira spp. *Treponema pallidum* is extremely sensitive to the bactericidal action of benzylpenicillin.

5.2 Pharmacokinetic properties

Intramuscular benzathine benzylpenicillin is absorbed very slowly into the bloodstream from the intramuscular site and converted by hydrolysis to benzylpenicillin. 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 225 mg of benzathine benzylpenicillin in adults results in blood levels of 22.5 to 37.5 nanogram per mL, which are maintained for 4 to 5 days. Similar blood levels may persist for 10 days following administration of 450 mg and for 14 days following administration of 900 mg. Blood concentrations of 2.25 nanogram per mL may still be detectable 4 weeks following administration of 900 mg.

Approximately 60% of benzylpenicillin 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. Benzylpenicillin 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.

5.3 Preclinical safety data

Carcinogenesis and Mutagenesis

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carmellose sodium
Sodium citrate
Water for injection
Lecithin
Povidone
Methyl hydroxybenzoate
Propyl hydroxybenzoate.

6.2 Incompatibilities

Not known.

6.3 Shelf life

48 months from date of manufacture stored at 2° to 8°C.

BICILLIN L-A may be stored below 30°C, for a single period of up to 2 months, prior to expiry. The date the product is placed outside of refrigerated storage and stored below 30°C should be written in the space provided on the carton. After storage outside of refrigeration, the product should be discarded and cannot be returned to refrigerated storage.

6.4 Special precautions for storage

Refrigerate, do not freeze.

6.5 Nature and contents of container

BICILLIN L-A is supplied as follows:

2.3 mL pre-filled glass syringe, containing 1,200,000 Units benzathine benzylpenicillin tetrahydrate, equivalent to 1016.6 mg; pack of 10 syringes.

6.6 Special precautions for disposal and other handling

Single dose injection. Use a single dose unit in one patient on one occasion only. Discard any unused portion.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited
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9. DATE OF FIRST APPROVAL

01 November 2012

10. DATE OF REVISION OF THE TEXT

5 November 2020

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2, 4.4	Sodium quantity added.
4.2, 4.4	Safety-related text added on avoiding administration in anterolateral thigh.
4.4	Change the name from *Clostridium difficile* to *Clostridioides difficile.*
4.4, 4.8	Safety-related changes relating to SCAR.
2, 4.4, 4.8, 8	Minor editorial changes.