SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

PENILENTE LA 1,2 MU Powder for suspension for injection

PENILENTE LA 2,4 MU Powder for suspension for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PENILENTE LA 1,2 MU contains ± 1 111,11 mg benzathine benzylpenicillin per vial.

PENILENTE LA 2,4 MU contains ± 2 222,22 mg benzathine benzylpenicillin per vial.

After reconstitution each dose of 2 mL suspension contains 600 000 units benzathine benzylpenicillin.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for suspension for injection.

Dry: White powder.

Reconstituted: White uniform suspension after mild agitation.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of infections caused by organisms sensitive to penicillin:

  staphylococci (except penicillinase-producing strains), streptococci (Groups A, C, G, H, L, and M), and pneumococci, *Corynebacterium diphtheriae, Bacillus anthracis,* Clostridia species, *Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes,* and Leptospira species.

- Streptococcal pharyngitis (Grade A betahaemolytic streptococci infection).
- Syphilis (Neisseria gonorrhoeae, Treponema pallidum) of less than 1 year duration.
- Uncomplicated cases of erysipeloid (*Erysipelothrix rhusiopathiae).*
- Prophylactic use: recurrence of rheumatic fever.

4.2 Posology and method of administration

Posology

Adults: Streptococcal pharyngitis and erysipeloid: 1,2 million units.

Syphilis: 2,4 million units.

Recurrence of rheumatic fever 1,2 million units.

Paediatric population

Children: 600 000 units to 1,2 million units.

Should be administered by deep intramuscular injection once a month.

Method of administration

FOR INTRAMUSCULAR USE ONLY.

Not for intravenous (IV) use.

See section 6.6 for preparation of suspension.

4.3 Contraindications

Must not be administered to patients who are allergic to penicillin or cephalosporins or to any ingredient of PENILENTE LA.

Babies in the neonatal period born to mothers allergic to penicillin.

Cases of cross-sensitivity to other beta-lactams have been reported. Should not be used in life-threatening conditions e.g., endocarditis, peritonitis or meningitis where very high doses of penicillin is indicated.

Must not be administered intravenously (IV).

4.4 Special warnings and precautions for use

FOR INTRAMUSCULAR USE ONLY.

PENIILENTE LA should not be used in tissues with reduced perfusion.

Before initiating therapy with PENILENTE LA, a careful investigation should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam medicines (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous reactions) have been reported in patients on penicillin therapy (i.e., PENILENTE LA). Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. If an allergic reaction occurs, PENILENTE LA must be discontinued and appropriate therapy instituted.

When administered to a patient with penicillin allergy, anaphylactic shock may occur. Epinephrine (adrenaline), corticosteroids, antihistamines and appropriate IV fluids should be used to treat anaphylaxis (see section 4.3).

Use with caution in patients with known history of allergy.

Prior to treatment, a hypersensitivity test should be performed if possible. The patient should be made aware of the

possible occurrence of allergic symptoms and of the need to report them.

Caution should be exercised in patients with the following conditions:

- Allergic diathesis or bronchial asthma (there is an increased risk of a hypersensitivity reaction);
- renal insufficiency;
- impaired hepatic function.

A generalised sensitivity reaction with urticaria, fever, joint pains and eosinophilia can develop within a few hours to several weeks after starting treatment.

Based on a general principle, particularly in some exposed patients, medical observation should if possible be ensured for at last half an hour after the administration of this antibiotic, as severe immediate allergic reactions may occur even after the first administration.

Beta-lactams are associated with a risk of encephalopathy (confusion, altered levels of consciousness, epilepsy or movement abnormalities), particularly in cases of over-dose or impaired renal function.

Care should be taken when high doses are given to patients with renal impairment (because of the risk of neurotoxicity) or congestive heart failure.

When treating syphilis, a Jarisch-Herxheimer reaction may occur as a result of the bactericidal action of penicillin on pathogens. This reaction can be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

Within 2 to 12 hours after administration headaches, fever, sweating, shivering, myalgia, arthralgia, nausea, tachycardia, increased blood pressure followed by hypotension may occur. These symptoms resolve after 10 to 12 hours. Patients should be informed that this is a usual, transient sequela of antibiotic therapy. Appropriate therapy

should be instituted to suppress or attenuate a Jarisch-Herxheimer reaction (see section 4.8).

With long-term treatment (more than a single dose), periodic assessment of organ system functions, including renal, hepatic, and haematopoietic function is recommended.

Prolonged use of PENILENTE LA may occasionally result in an overgrowth of non-susceptible organisms or yeast and patients should be observed carefully for superinfections. Superinfection by resistant species, such as *Pseudomonas* or *Candida*, which do not respond to penicillin therapy, may occur.

Antibiotic-associated colitis has been reported with nearly all antibacterial medicines including PENILENTE LA and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, benzathine benzylpenicillin (i.e., PENILENT LA) should be discontinued, a medical practitioner be consulted, and an appropriate therapy initiated. Anti-peristaltic medicines are contraindicated in this situation.

If neurological involvement cannot be excluded in patients with congenital syphilis, forms of penicillin that reach a higher level in cerebrospinal fluid should be used.

In diseases such as severe pneumonia, empyema, sepsis, meningitis, or peritonitis, which require higher serum penicillin levels, alternative treatment such as the water-soluble alkali salt of benzylpenicillin should be considered.

Notes on administering PENILENTE LA

Painful induration may occur in the event of accidental subcutaneous administration. Ice packs help in such cases.

Care should be taken to avoid accidental intravascular injection.

In the event of accidental intravascular injection of PENILENTE LA, Hoigné syndrome (a non-allergic clinical syndrome) may occur. This is characterised by symptoms of shock, anxiety, agitation, psychotic reactions including visual and auditory disturbances (confusion and hallucinations), seizures, tachycardia and hypertension, cyanosis, a sensation of impending death or symptoms of mortal fear, and motor disorders, although no circulatory collapse, caused by micro emboli of the suspension. The symptoms regress within an hour. If progression is severe, parenteral administration of sedatives is indicated.

Disturbances of blood electrolytes may follow the administrations of large doses of PENILENTE LA.

In the event of inadvertent intra-arterial injection, particularly in children, serious complications may occur, such as vascular occlusion, thrombosis, and gangrene. Initial signs are pale patches in the skin area of the gluteal region. As a result of high injection pressure, retrograde entry of the injected liquid into the common iliac artery, aorta or spinal arteries may occur.

Repeated injections into a limited area of the muscle tissue, which are associated with long term therapy with depot-penicillins (e.g., in the treatment of syphilis) may induce tissue damage and increased local vascularization. Subsequent injections increase the possibility of penetration of injection substance into the blood, either by direct injection into a blood vessel or caused by the injection pressure itself, or by “rubbing” of the depot. During long term therapy it is therefore recommended to administer each injection a large distance from the preceding injection.

Effect on diagnostic laboratory procedures

- A positive direct Coombs' test often develops (≥ 1 % to < 10 %) in patients receiving 10 million IU (equivalent to 6 g) benzylpenicillin or more per day. After discontinuation of the penicillin, the direct antiglobulin test may remain positive for 6 to 8 weeks (see section 4.8).
- Determination of urinary protein using precipitation techniques (sulphosalicylic acid, trichloroacetic acid), the

Folin-Ciocalteu-Lowry method or the biuret method may lead to false positive results. Urinary protein should therefore be determined by other methods.

- Urinary amino acid determination using the ninhydrin method may likewise lead to false-positive results.
- Penicillins bind to albumin. In electrophoresis methods to determine albumin, pseudobisalbuminaemia may therefore be simulated.
- During therapy with PENILENTE LA, non-enzymatic urinary glucose detection and urobilinogen detection may exhibit a false positive.
- When determining 17-ketosteroids (using the Zimmermann reaction) in the urine, increased values may occur during therapy with PENILENTE LA.

Excipients

PENILENTE LA Powder for suspension for injection contains phospholipids from the soya lecithin. If you are allergic to peanut or soya, do not use this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per vial, i.e., essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of PENILENTE LA is not recommended with:

- *Bacteriostatic antibiotics:* based on the general principle not to combine bactericidal and bacteriostatic antibiotics.

Caution should be exercised when co-administering the following:

- *Probenecid:* the administration of probenecid leads to inhibition of the tubular secretion of benzylpenicillin, resulting in an increase in the serum concentration and prolongation of the elimination half-life. Furthermore, probenecid inhibits the penicillin transport from the cerebrospinal fluid, so that the concomitant administration

of probenecid reduces the penetration of benzylpenicillin into brain tissue even further.

- *Methotrexate:* when taken at the same time as PENILENTA LA, the excretion of methotrexate is reduced. This can lead to increased methotrexate toxicity. The combination with methotrexate is not recommended.
- *Anticoagulants:* concomitant use with oral anticoagulants, such as warfarin and PENILENTE LA , may increase the anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently, and the posology of the anti-vitamin K medicine adjusted accordingly, both during and after treatment with PENILENTE LA.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and/or efficacy during pregnancy has not been established.

Breastfeeding

Mothers on PENILENTE LA should not breastfeed their infants.

Safety and/or efficacy during lactation has not been established.

Fertility

No fertility studies have been conducted in humans.

4.7 Effects on the ability to drive and use machines

Due to the occurrence of possible serious undesirable effects (e.g., anaphylactic shock with collapse and anaphylactoid reactions, see also section 4.8), PENILENTE LA can have a major influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent and common adverse reactions related to -benzathine benzylpenicillin (i.e., PENILENTE LA) are candidiasis, diarrhoea, nausea, and laboratory investigation changes.

b. Tabulated list of adverse reactions

MedDRA System Organ Class (SOC)	**Frequent**	**Less frequent**	**Frequency unknown**
Infections and infestations	Candidiasis.		
Blood and lymphatic system disorders		Leukopenia, thrombocytopenia, agranulocytosis.	Haemolytic anaemia, neutropenia, prolongation of bleeding time, defective platelet function.
Immune system disorders	Allergic reactions which may include exfoliative dermatitis, other skin rashes, and vasculitis, may occur.	Angioedema, erythema multiform, arthralgia, anaphylactic shock with collapse and anaphylactoid reactions (asthma, purpura, gastrointestinal).	Serum sickness, a generalised sensitivity reaction with urticaria, fever, joint pains and eosinophilia, superinfection by resistant species, Jarisch-Herxheimer reaction.
Cardiac disorders			Kounis syndrome.
Gastrointestinal disorders	Diarrhoea, nausea, stomatitis and glossitis,		Heartburn, pseudo-membranous colitis (see

	vomiting.		section 4.4).
Hepato-biliary disorders			Hepatitis, cholestasis, increases in liver enzyme values.
Skin and subcutaneous tissue disorders		A sore mouth or tongue and a black hairy tongue.	Linear immunoglobulin A (IgA) disease.
Renal and urinary disorders		Nephropathy, interstitial nephritis.	
General disorders and administration site conditions			Pain at the injection site, injection site infiltrates, Hoigné syndrome, Nicolau syndrome.
Investigations	Positive direct Coombs' test. False-positive urinary protein determination when precipitation techniques are used (Folin- Ciocalteu-Lowry method, biuret method). False-positive urinary amino acid determination (ninhydrin method). Simulation of Pseudobisal buminaemia when using		

	electrophoresis methods to determine albumin. False-positive nonenzymatic urinary glucose detection and urobilinogen detection. Increased levels when determining 17 ketosteroids in urine (when the Zimmermann reaction is used) (see section 4.4).		

c. Description of selected adverse reactions

When treating syphilis, a Jarisch-Herxheimer reaction may occur as a result of bacteriolysis, characterised by fever, chills, general and focal symptoms. In patients with dermatomycosis, para-allergic reactions may occur, as common antigenicity may exist between penicillins and dermatophyte metabolites.

In infants, local reactions are possible.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

At extremely high doses, penicillins can induce neuromuscular excitability or epileptiform seizures. If overdose is suspected, supportive treatment and symptomatic measures are indicated. Benzylpenicillin can be haemodialyzed. In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.2 Penicillins

Pharmacotherapeutic group: Antibacterials for systemic use, beta-lactamase sensitive penicillins.

ATC code: J01CE08

Benzathine benzylpenicillin, as contained in PENILENTE LA, is a betalactamase antibiotic that is bactericidal by inhibition of cell wall synthesis and is broken down by penicillinase.

Resistant microorganisms:

Aerobic Gram-positive microorganisms: *Coagulase negative Staphylococcus, Enterococcus Spp, Staphylococcus aureus.*

Aerobic Gram-negative microorganisms: *Acinetobacter, Bordetella pertussis, Brucella spp., Enterobacteriaceae (including Escherichia coli, Salmonella, Shigella, Enterobacter, Klebsiella, Proteus, Citrobacter), Haemophilus influenza, Pseudomonas.*

Anaerobic microorganisms: *Bacteroides fragilis.*

Known resistance mechanisms and cross-resistance

Penicillin resistance can be mediated by alteration of penicillin binding proteins or development of beta-lactamases.

Resistance to penicillin may be associated with cross-resistance to a variety of other beta-lactam antibiotics either due to a shared target site that is altered, or due to a beta-lactamase with a broad range of substance molecules. In addition to this, cross-resistance to unrelated antibiotics can develop due to more than on resistance gene being present on a mobile section of DNA (e.g., plasmid, transposon etc.) resulting in two or more resistance mechanisms being transferred to a new organism at the same time.

5.2 Pharmacokinetic properties

Benzathine benzylpenicillin has an extremely low solubility and is slowly released from intramuscular injection sites. Benzathine benzylpenicillin is hydrolysed 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 300 000 units of benzathine benzylpenicillin in adults results in blood levels of 0,03 to 0,05 units per mL, which are maintained for 4 to 5 days. Similar blood levels may persist for 10 days following administration of 600 000 units and for 14 days following administration of 1 200 000 units. Blood concentrations of 0,003 units per mL may still be detectable 4 weeks following administration of 1 200 000 units.

Approximately 60 % of benzylpenicillin is bound to serum protein. It 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, it is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate buffer 9,23 % *w/w*

Lecithin

Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool, dry place, at or below 25 °C.

Suspensions must be used within 4 weeks when stored at or below 25 °C.

6.5 Nature and contents of container

PENILENTE LA 1,2 MU (Powder for suspension for injection) - 10 x 10 mL vials containing a white powder which after reconstitution yields a 4 mL suspension.

PENILENTE LA 2,4 MU (Powder for suspension for injection) - 10 x 10 mL vials containing a white powder which after reconstitution yields an 8 mL suspension.

6.6 Special precautions for disposal and other handling

Preparation of suspension

Distribute the contents evenly by tapping the vial lightly. Add Water for Injection and shake the vial vigorously. Within a few minutes the suspension will reach its maximum viscosity and the insoluble penicillin will then be uniformly suspended.

a) 1,2 mu vial: Add 3,5 mL Water for Injection. This will yield a suspension allowing 1,2 mega units in 4 mL to

be withdrawn.

b) 2,4 mu vial: Add 7 mL Water for Injection. This will yield a suspension allowing 2,4 mega units in 8 mL to be withdrawn.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Block K West, Central Park

400 16th Road, Halfway House

Midrand

1685

8 REGISTRATION NUMBER(S)

PENILENTE LA 1,2 MU: A/20.1.2/435

PENILENTE LA 2,4 MU: A/20.1.2/823

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 28 June 1997

10 DATE OF REVISION OF THE TEXT

31 January 2025.