Applicant/HCR	Biotech Laboratories (Pty) Ltd.
Proprietary Name:	Bio-Pen 1 MU & Bio-Pen 5 MU
Registration number:	A/20.1.2/444 & A/20.1.2/825
Dosage Form & Strength:	Injection. Each vial contains 600 mg (1 MU) or 3 g (5 MU) benzylpenicillin sodium, respectively.

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

BIO-PEN 1 MU powder for solution for injection

BIO-PEN 5 MU powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BIO-PEN 1 MU: Each vial contains benzylpenicillin sodium 600 mg (1 million units)

BIO-PEN 5 MU: Each vial contains benzylpenicillin sodium 3 g (5 million units)

Excipient with known effect:

Sodium citrate buffer: 4,3 % *w/w*

BIO-PEN 1 MU: Each vial contains 47,2 mg of sodium.

BIO-PEN 5 MU: Each vial contains 235,9 mg of sodium.

BIO-PEN is sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection

Dry powder: White crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BIO-PEN is indicated in the treatment of infections caused by benzylpenicillin sensitive microorganisms, listed below, when rapid and high penicillinaemia is required:

- *Streptococcus pyogenes* (group A betahemolytic streptococcus), other betahemolytic streptococci including groups C, H, G, L and M, *Streptococcus pneumoniae* and *Staphylococcus* species (non-penicillinase producing strains).
- *Bacillus anthracis*
- *Actinomyces Israelil*
- *Clostridium* species
- *Corynebacterium diphtheriae*
- *Erysipelothrix rhusiopthiae*
- *Fusobacterium species* and spirochetes
- *Listeria monocytogenes*
- *Pasteurella multocida*
- *Streptobacillus moniliformis*
- *Spirillum minus* or *Streptobacillus moniliformis*
- *Leptospira*
- *Neisseria gonorrhoeae* – penicillin susceptible
- *Neisseria meningitidis*
- *Treponema pallidum*

- *Borrelia burgdorferi* (Lyme disease)
- Gram-negative bacillary infections (bacteremias) (*Escherichia coli, Enterobacter aerogenes, Alcaligenes faecalis, salmonella, shigella* and *Proteus mirabilis).* Many *E. coli* and *Proteus mirabilis* strains are susceptible to high concentrations.

Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

Prophylactic use:

Prevention of recurrence of rheumatic fever;

Prophylaxis of infective endocarditis in patients with valvular heart disease undergoing surgical procedures.

4.2 Posology and method of administration

Posology

Adults:

500 000 – 20 million units daily preferably in divided doses.

Severe infections:

Such as meningitis, endocarditis and peritonitis 20 million units daily.

Children:

10 000 – 50 000 units per kg body mass per 24 hour period, divided in 4 doses.

Severe infections:

300 000 – 400 000 units/kg/day.

Neonates:

50 000 units per kg body mass per day in divided doses.

Severe infections:

50 000 – 200 000 units/kg/day.

In the treatment of beta-haemolytic streptococcal infections a therapeutic dose must be administered for at least 10 days.

Prophylactic use

Prevention of recurrence of rheumatic fever: 200 000 units intramuscularly twice daily.

Patients with valvular heart disease undergoing surgery:

Adults:

2 million units intravenously or intramuscularly 30 to 60 minutes preoperatively and 1 million units six hours later.

Children:

50 000 units per kg body mass 30 to 60 minutes preoperatively and 25 000 units per kg body mass six hours later.

Method of administration

For intravenous (injection or infusion), or intramuscular administration.

To be dissolved in water for injection – see dilution table included.

Reconstituted product: Clear, colourless to yellowish solution free of particulate matter

Where doses of 2 million units or more are required, these should be administered by slow intravenous infusion at a rate of less than 500 000 units per minute, or by intermittent piggy-back infusion.

For information on instructions for preparation or reconstitution see section 6.6.

4.3 Contraindications

Hypersensitivity to benzylpenicillin or to any of the excipients of BIO-PEN listed in section 6.1.

Known allergy to penicillin or cephalosporins. Cases of cross sensitivity have been reported.

Babies born of allergic mothers in the neonatal period.

4.4 Special warnings and precautions for use

In cases of cephalosporin hypersensitivity, a cross-allergy is possible.

When administered to a patient with penicillin sensitivity, anaphylactic shock may occur. Adrenaline, corticosteroids and antihistamines should be used to treat anaphylaxis.

Prior to treatment, a hypersensitivity test should be carried out. Patients should be informed about the possible occurrence of a hypersensitivity reaction.

Use with caution in patients with known history of allergy. Patients with a history of allergy, especially to medicines, may be more prone to developing a hypersensitivity reaction to BIO-PEN. Observation of patients for 30 minutes after administration of BIO-PEN is recommended.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous reactions) have been reported in patients on penicillin therapy. 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, BIO-PEN therapy must be discontinued and appropriate

alternative therapy instituted.

Severe cutaneous adverse reactions (SCAR), including 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 association with beta-lactam antibiotics (including penicillins e.g., BIO-PEN) treatment (see section 4.8).

BIO-PEN is contraindicated in patients who are hypersensitive to penicillins. Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to benzylpenicillin (see section 4.3). BIO-PEN should not be used at all in patients with history of severe hypersensitivity reactions. If a severe allergic reaction or SCAR occurs during treatment with benzylpenicillin, treatment with BIO-PEN should be discontinued and appropriate measures taken.

Caution should be exercised in patients with the following conditions:

- allergic diathesis (urticaria or hay fever) or asthma (increased risk of hypersensitivity reactions)
- severe heart conditions (such as congestive heart failure) or severe electrolyte disturbances of any other origin (attention should be paid to electrolyte intake in this patient group, especially potassium intake)
- patients with renal impairment (because of the risk of neurotoxicity)
- liver damage
- epilepsy, cerebral oedema or meningitis and coma (increased risk of seizures, especially with high-dose administration (12 000 mg) of BIO-PEN; see section 4.8) when impaired renal function exists.
- existing mononucleosis (increased risk of skin rash)
- when treating co-infections in patients with acute lymphatic leukaemia (increased risk of skin reactions)
- dermatomycoses (para-allergic reactions are possible, as there may be common antigenicity between

penicillins and metabolic products of dermatophytes; see section 4.8).

In venereal diseases, dark field examinations should be performed before the start of therapy if co-existing syphilis is suspected. Serological tests for monitoring purposes should also be performed for at least 4 months.

Care should be taken when treating patients with syphilis, as the Jarisch-Herxheimer reaction may occur shortly after starting treatment. This reaction, manifesting as fever, chills, headache and reactions at the site of the lesion, can be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

Prolongation of the prothrombin time has been reported in patients receiving penicillins as contained in BIO-PEN. Appropriate monitoring should be performed when anticoagulants are co-administered. Adjustment of the oral anticoagulant dose may be necessary to obtain the desired degree of anticoagulation (see sections 4.5 and 4.8).

Intrathecal administration of penicillins, including BIO-PEN, is not recommended because it is a potent convulsant when given by this route.

With the concomitant administration of BIO-PEN and oral contraceptives the efficacy of oral contraceptives may be impaired; this may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

In diabetic patients the absorption from an intramuscular depot may be delayed.

Superinfections may occur with the prolonged use of BIO-PEN resulting from the overgrowth of non-susceptible organisms or yeast such as *Clostridium difficile* and *Candida*. Patients should be carefully observed for superinfections.

Antibiotic-associated pseudomembranous colitis should be considered in patients who develop severe and persistent diarrhoea (mucohaemorrhagic, watery diarrhoea, dull, diffuse to colicky abdominal pain, fever, occasionally tenesmus), which may be life-threatening, during or after receiving benzylpenicillin. In this situation, even if *Clostridium difficile* is only suspected, administration of BIO-PEN should be discontinued and appropriate treatment given.

For conditions such as severe pneumonia, empyema, sepsis, meningitis or peritonitis, which require higher serum penicillin levels, treatment with the water-soluble alkali salt of benzylpenicillin should be instituted.

Severe local reactions can occur with intramuscular administration to infants. If possible, intravenous therapy should be performed.

When intravenously administering very high doses (above 6 000 mg/day), the administration site should be alternated every other day to avoid superinfections and thrombophlebitis.

Due to possible electrolyte disturbances, BIO-PEN should be administered slowly with infusions of more than 6 000 mg and, due to the possibility of seizure reactions, when administering more than 12 000 mg (see section 4.8).

In prolonged treatment (more than 5 days) with high penicillin doses, monitoring of the electrolyte balance

(hypokalaemia and hypernatraemia), blood count monitoring, electrolyte balance and renal function tests are recommended. The use of a potassium-sparing diuretic may be helpful.

Effect on diagnostic laboratory procedures:

- A positive direct Coombs' test often develop in patients receiving 6 000 mg benzylpenicillin or more per day. Upon discontinuation of the penicillin, the direct antiglobulin test may still remain positive for 6 to 8 weeks (see section 4.5 and 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. Caution should therefore be exercised when interpreting the results of such tests in patients receiving BIO-PEN. Protein determination with test strips is not affected.
- Equally, urinary amino acid determination using the ninhydrin method may lead to false-positive results.
- Penicillins bind to albumin. In electrophoresis methods to determine albumin, pseudobisalbuminaemia may thereby be simulated.
- False-positive non-enzymatic urinary glucose detection and urobilinogen detection
- During therapy with BIO-PEN, non-enzymatic urinary glucose detection and urobilinogen detection may prove false-positive. Enzymatic urine glucose tests should be used in patients on therapy with BIO-PEN, as these are not affected by this interaction.
- When determining 17-ketosteroids (using the Zimmermann reaction) in urine, increased values may occur during therapy with BIO-PEN.

Skin contact with BIO-PEN should be avoided since skin sensitisation may occur.

Sodium content

BIO-PEN 1 MU contains 45,7 mg sodium per vial, equivalent to 2,3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

BIO-PEN 5 MU contains 224,7 mg sodium per vial, equivalent to 11,2 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicines and other forms of interaction

Concomitant administration of BIO-PEN is not recommended with:

Based on the general principle not to combine bactericidal and bacteriostatic antibiotics, BIO-PEN should not be combined with bacteriostatic antibiotics.

Caution is required when co-administering with:

Probenecid: Administration of probenecid leads to an inhibition of the tubular secretion of benzylpenicillin, resulting in an increase in 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.

Anti-inflammatories, antirheumatics and antipyretics: When co-administering BIO-PEN with anti-inflammatories, antirheumatics or antipyretics (especially indomethacin, phenylbutazone, salicylates at high doses), it should be pointed out that excretion is competitively inhibited, resulting in an increase in serum concentration and prolongation of the elimination half-life.

Digoxin: In patients on digoxin treatment, BIO-PEN should only be used with caution, as there is a risk of bradycardia as a result of interactions.

Oral contraceptives: With the concomitant administration of BIO-PEN and oral contraceptives the efficacy of oral contraceptives may be impaired; this may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

Methotrexate: BIO-PEN may lead to the reduced excretion of methotrexate and therefore increased risk of methotrexate toxicity. Concomitant use of methotrexate and penicillin should be avoided if possible. If concomitant use is unavoidable, a reduction in the methotrexate dose should be considered and methotrexate serum levels should be monitored. The patient should be monitored for possible additional adverse reactions of methotrexate, including leukopenia, thrombocytopenia and skin suppuration.

Oral anticoagulants: Oral anticoagulants and penicillin antibiotics have been used extensively in practice without interactions. However, in the literature, there are reports of an increased number of patients who experienced a bleeding event when they were prescribed acenocoumarol or warfarin at the same time as penicillin such as BIO-PEN. If concomitant use is required, the prothrombin time or other suitable coagulation parameters should be carefully monitored upon co-administration or discontinuation of penicillin (e.g., BIO-PEN). Furthermore, an adjustment of the oral anticoagulant dose may be necessary (see sections 4.4 and 4.8).

Synergism between antibiotics:

BIO-PEN should only be given in combination with other antibiotics if a synergistic or at least an additive effect is anticipated. In general, the individual components of a combination must be given at the full effective dose (exception: if synergism is proven, the dose of the more toxic combination partner can be reduced).

If duly indicated, BIO-PEN can be combined with the following bactericidal antibiotics:

- isoxazolyl penicillins (e.g. flucloxacillin and other narrow-spectrum beta-lactams)

- aminopenicillins

- aminoglycosides

The above-mentioned penicillins are given by slow intravenous injection prior to the BIO-PEN infusion. Wherever possible, aminoglycosides should be given separately via the intramuscular route.

4.6 Fertility, pregnancy, and lactation

Pregnancy

Safety in pregnancy has not been established.

An increase in malformations or other direct or indirect harmful effects on the foetus have not been observed with use of benzylpenicillin, as contained in BIO-PEN, in pregnant women and women of childbearing age.

Breastfeeding

Safety in lactation has not been established.

BIO-PEN is excreted into breast milk.

Fertility

No studies have been performed to investigate the effect of benzylpenicillin as contained in BIO-PEN on fertility.

4.7 Effects on 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), BIO-PEN can have an influence on the ability to drive and use

machines.

4.8 Undesirable effects

Infections and infestations	
Frequency unknown:	Superinfection by resistant species, such as *Pseudomonas* or *Candida*, which do not respond to penicillin therapy.
Blood and lymphatic system disorders	
Less frequent:	Haemolytic anaemia and granulocytopenia (neutropenia), agranulocytosis, leucopenia and thrombocytopenia, have been reported in patients receiving prolonged high doses of benzylpenicillin sodium (e.g. subacute bacterial endocarditis), eosinophilia, pancytopenia, coagulation disorders.
Frequency unknown:	Prolongation of the bleeding time and prothrombin time (see section 4.4).
Immune system disorders	
Frequent:	Patients undergoing treatment for syphilis or neurosyphilis with benzylpenicillin may develop a Jarisch-Herxheimer reaction. Hypersensitivity reactions including exfoliative dermatitis, other skin rashes, vasculitis, fever, and serum sickness. A generalised sensitivity reaction with urticaria, fever, joint pains and eosinophilia can develop within a few hours to several weeks after starting treatment.
Less frequent:	Allergic reactions, erythema multiforme, arthralgia (joint stiffness), anaphylaxis or anaphylactoid reactions (asthma, purpura, gastrointestinal symptoms). Para-allergic reactions may occur in patients with dermatomycoses, as there may be common antigenicity between penicillins and metabolic products of

	dermatophytes.
Frequency unknown:	Angioedema.
Metabolism and nutrition disorders	
Less frequent:	Electrolyte imbalances may occur upon rapid infusion of more than 6 000 mg,
Nervous system disorders	
Less frequent:	Central nervous system toxicity, neuropathy. Convulsive reactions may occur upon infusion of high doses (in adults, more than 12 000 mg); this should be particularly borne in mind in patients with severely impaired renal function, epilepsy, meningitis, cerebral oedema or during cardiopulmonary bypass.
Frequency unknown:	Metabolic encephalopathy.
Cardiac disorders	
Frequency unknown:	Kounis syndrome
Gastrointestinal disorders	
Frequent:	Diarrhoea, nausea, heartburn.
Less frequent:	Sore mouth or tongue, a black hairy tongue, vomiting. Diarrhoea caused by *Clostridium difficile.* If diarrhoea develops during treatment, the possibility of pseudomembranous colitis should be considered (see section 4.4).
Hepato-biliary disorders	
Less frequent:	Increases in liver enzyme values.
Frequency unknown:	Hepatitis, cholestasis.
Skin and subcutaneous tissue disorders	
Frequency unknown:	Pemphigoid, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN),

	drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), pruritus, maculo-papular rash, rash morbilliform, erythema, linear IgA disease.
Renal and urinary disorders	
Less frequent:	Interstitial nephritis, nephropathy (after intravenous administration of more than 6 000 mg benzylpenicillin albuminuria, cylindruria and haematuria, oliguria or anuria, which can less frequently occur during high-dose penicillin therapy, generally disappears within 48 hours upon discontinuation of treatment. Diuresis can also be stimulated with 10 % mannitol solution.
General disorders and administration site conditions	
Less frequent:	Severe local reactions during intramuscular administration to infants.
Investigations	
Frequent:	– positive direct Coombs' test, – false-positive urinary protein determination using precipitation techniques (Folin-Ciocalteu-Lowry method, Biuret method), – false-positive urinary amino acid determination (ninhydrin method), falsification of pseudobisalbuminaemia when using electrophoresis methods to determine albumin, – false-positive non-enzymatic urinary glucose detection and urobilinogen detection, – increased values when determining 17-ketosteroids in urine (using the Zimmermann reaction) (see section 4.5).

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Increased neuromuscular hyperexcitability or susceptibility to cerebral seizures can be anticipated in the event of an overdose. Countermeasures: discontinuation, clinical surveillance and symptomatic treatment.

Excessive blood levels of BIO-PEN can be corrected by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.20.1.2 Penicillins.

Pharmacotherapeutic group: Benzylpenicillin (penicillin G) is a semi-synthetic, beta-lactamase-sensitive, beta-lactam antibiotic. ATC code: J01CE01

Benzylpenicillin has a broad range of activity against Gram+ and Gram- micro-organisms.

IN-VITRO SENSITIVITY DOES NOT NECESSARILY IMPLY *IN-VIVO* EFFICACY.

A meningococcal carrier state is not eliminated.

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.*

5.2 Pharmacokinetic properties

Absorption:

Benzylpenicillin is not acid-stable and can therefore only be administered parenterally. The alkali salts of benzylpenicillin are rapidly and completely absorbed after IM injection.

Peak plasma levels of 0,09 - 0,12 mg/mL are reached 15 - 30 min. after IM injection of 6 000 mg Benzylpenicillin. After a short infusion (30 min.), peak levels of up to 0,3 mg/mL may be reached. About 55 % of the administered dose is bound to plasma proteins.

Distribution:

Benzylpenicillin is widely distributed throughout the body. Significant amounts appear in the liver, bile, semen, joint fluid, lymph and intestines. It becomes reversibly bound to plasma proteins.

Biotransformation and elimination:

Elimination occurs largely (50 – 80 %) as unchanged substance via the kidneys (85 – 95 %) and, to a lesser degree, inactive form with the bile (approximately 5 %).

The half-life of benzylpenicillin is only 30 minutes. It is normally rapidly eliminated from the body, mainly by the kidneys.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate (pH buffer)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened vial: 4 years

After reconstitution:

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

The buffered solution must be used within 7 days if stored at 4 - 8 °C or within 2 days at temperatures approaching 25 °C.

6.4 Special precautions for storage

Store in a dry place at or below 25 °C (dry powder).

For storage conditions after reconstitution of BIO-PEN, see section 6.3.

6.5 Nature and contents of container

BIO-PEN 1 MU: 10 or 100, vials containing a white crystalline powder which after reconstitution yields a 5 ml solution.

Pack size: 10 or 100 vials.

BIO-PEN 5 MU: 50 vials containing a white crystalline powder which after reconstitution yields a 10 ml solution.

Pack size: 50 vials.

6.6 Special precautions for disposal and other handling

Any unused BIO-PEN or waste material should be disposed of in accordance with local requirements.

DILUTION TABLE 600 mg (1 Mu) Vial	
ADDITION OF STERILE WATER	
Concentration	Add
200 000 units per mL	4,6 mL
500 000 units per mL	3,6 mL
1 million units per 2 mL	1,6 mL
1 million units per 5 mL	4,6 mL

DILUTION TABLE 3 g (5 Mu) Vial	
ADDITION OF STERILE WATER	
Concentration	Add
250 000 units per mL	17,8 mL
500 000 units per mL	7,8 mL
2 million units per 5 mL	10,4 mL
5 million units per 10 mL	7,8 mL

The reconstituted solution is clear, colourless to yellowish and free of particulate matter.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Block K West, Central Park

400 16th Road

Randjespark

Midrand

1685

8 REGISTRATION NUMBERS

BIO-PEN 1 MU – A/20.1.2/444

BIO-PEN 5 MU – A/20.1.2/825

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of registration: 22 September 1994

10 DATE OF REVISION OF THE TEXT

04 December 2024.