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.

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS: S4

BIO-PEN 1 MU, benzylpenicillin sodium, powder for solution for injection.

BIO-PEN 5 MU, benzylpenicillin sodium, powder for solution for injection.

B**enzylpenicillin sodium**

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.

Read all of this leaflet carefully before you are given BIO-PEN

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor, pharmacist, nurse, or other healthcare provider.
- BIO-PEN has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.

What is in this leaflet

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1. What BIO-PEN is and what it is used for

The active substance is benzylpenicillin sodium.

BIO-PEN is an antibiotic and used in the treatment of infections caused by sensitive microorganisms, listed below:

- *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.

BIO-PEN is also used to prevent the recurrence of rheumatic fever and to prevent infection of the heart tissues (e.g. heart valves) in patients with valvular heart disease undergoing surgery.

2. What you need to know before you are given BIO-PEN

BIO-PEN should not be administered to you:

- If you are hypersensitive (allergic) to benzylpenicillin, any other antibiotics namely penicillin or cephalosporins, or any of the other ingredients of BIO-PEN (listed in section 6).
- If your baby requires treatment and you (the mother) are allergic to antibiotics (penicillin or cephalosporins).

Warnings and precautions

Special care should be taken with BIO-PEN:

- If you are sensitive to penicillin you may have anaphylactic shock, which is a very serious allergic reaction, if you receive BIO-PEN. This is [~~a~~**]** life-threatening. The signs include sudden swelling of the throat or face which might make it difficult to breath or swallow, sudden swelling of the hands, feet and ankles, chest pain and a severe rash that develops quickly.
- If you have a history of allergies, especially to medicines, inform your doctor of any allergies you may have. Your doctor or healthcare provider will monitor you when administering BIO-PEN and administer the necessary treatment if an allergic reaction occurs.
- Serious skin reactions such as toxic epidermal necrolysis (TEN), Steven-Johnson syndrome (SJS),

acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with in patients using certain antibiotics such as BIO-PEN. If you experience any signs of serious skin reactions such as swelling, itching, red severe rash, stop using BIO-PEN immediately and contact your doctor (see section 4).

- If you have kidney problems or heart failure and receive high doses of BIO-PEN, seizures and coma may occur. Tell your doctor if you have existing kidney **[**~~of~~**]** or heart problems.
- If you are prone to allergic reactions (such as nettle-rash or hay fever) or asthma. In such cases, there is an increased risk of allergic reactions.
- If you have a heart condition or severe electrolyte disorders, such as of sodium, calcium, potassium, chloride. Your doctor should monitor your intake of electrolytes, especially your potassium intake.
- If you have liver problems.
- If you have a glandular fever, called mononucleosis. There is an increased risk of skin reactions.
- If you have a cancer of white blood cells, called acute lymphatic leukaemia, there is an increased risk of skin reactions.
- If you have a fungal skin disease. You are at increased risk of developing allergy-like reactions.
- If you have a sexually transmitted disease and syphilis. Your doctor will perform tests before starting and during treatment.
- If you are being treated for syphilis you may have a reaction known as Jarisch-Herxheimer shortly after starting treatment with BIO-PEN which may manifest as fever, chills, headache and reactions at the site of the lesion, low blood pressure, increased heart rate and flushing. This reaction may be dangerous if you have cardiovascular syphilis or if your nervous system is affected by syphilis. Tell your doctor if you notice any of the above.
- If you have diabetes the effect of BIO-PEN may be delayed when injected into a muscle.

- If you require prolonged treatment with BIO-PEN you may develop other infections such as yeast or bacterial infections, if you experience recurring infections or experience symptoms such as fever, diarrhoea, abdominal discomfort or thrush, report it to your doctor, your doctor will monitor your condition.
- If you develop pseudomembranous colitis, an infection due to the overgrowth of bacteria that is not susceptible to BIO-PEN, if you experience symptoms such as persistent diarrhoea (bloody, mucous to watery), abdominal cramps, fever or nausea, notify your doctor, your doctor may decide to discontinue your treatment.
- Penicillin in BIO-PEN can cause blood to clot more slowly. If you're also taking blood thinners, your doctor should monitor your blood and may need to change your blood thinner dose.
- If you are receiving very high doses through an IV, change the site every other day to prevent infections and vein problem.
- BIO-PEN can cause skin sensitisation. Skin contact should be avoided.
- If you have to undergo a laboratory test. BIO-PEN can interfere with the results of certain urine and blood tests. Therefore, inform your doctor before any laboratory test is performed about your treatment with BIO-PEN.

Children

Severe local reactions may occur in infants upon administration into the muscle. Therefore, injection into a vein for this age group should be performed wherever possible.

Other medicines and BIO-PEN

Always tell your healthcare provider if you are taking any other medicines. (This includes all complementary or traditional medicines).

BIO-PEN can cause interactions when used with other medicines:

- Other medicines to treat bacterial infections. BIO-PEN only act on certain bacteria. Therefore, this medicine should only be combined with other medicines to treat bacterial infections as decided by the doctor.
- Indomethacin, phenylbutazone, acetylsalicylic acid and similar medicines to reduce fever, inflammation, rheumatic disorders and pain.
- Digoxin: to treat heart weakness.
- The effectiveness of oral contraceptives may be reduced by BIO-PEN which can lead to unwanted pregnancy. Ask your healthcare provider about alternative contraception methods.
- The side effects of methotrexate (medicine used in the treatment of cancer, psoriasis and rheumatoid arthritis) may be increased by BIO-PEN.
- The effect of BIO-PEN may be increased by probenecid (medicine used in the treatment of gout).
- Medicines taken orally to inhibit blood coagulation, such as acenocoumarol, warfarin. If combined use is required, suitable blood-clotting parameters should be carefully monitored during and after stopping treatment with this medicine. A dose adjustment of the medicine to inhibit blood coagulation may be necessary.

Pregnancy, breastfeeding and fertility

The safe use of BIO-PEN during pregnancy and breastfeeding has not been established.

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before receiving BIO-PEN.

BIO-PEN is excreted into breast milk.

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

fertility.

Driving and using machines

BIO-PEN can cause possible serious side effects, like severe allergic reactions, which can have an influence on your ability to drive and use machines. Do not drive or use machines if you get serious side effects.

It is not always possible to predict to what extent BIO-PEN may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which BIO-PEN affects them.

BIO-PEN contains sodium

BIO-PEN 1 MU contains 45,7 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2,3 % of the recommended maximum daily dietary intake of sodium for an adult.
BIO-PEN 5 MU contains 224,7 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 11,2 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How BIO-PEN is given

Do not share medicines prescribed for you with any other person.
You will not be expected to give yourself BIO-PEN. It will be given to you by a person who is qualified to do so.
BIO-PEN can be injected into a muscle or a vein.

Your doctor will determine your dose and tell you how long your treatment with BIO-PEN will last.

If you have the impression that the effect of BIO-PEN is too strong or too weak, tell your doctor or pharmacist.

If you are administered more BIO-PEN than you should

Since a healthcare provider will administer BIO-PEN, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If a dose of BIO-PEN is missed

Since a healthcare provider will administer BIO-PEN, it is unlikely that the dose will be missed.

4. Possible side effects

BIO-PEN can have side effects.

Not all side effects reported for BIO-PEN are included in this leaflet. Should your general health worsen or if you experience any untoward effects while receiving BIO-PEN, please consult your healthcare provider for advice.

If any of the following happens, stop receiving BIO-PEN and tell your doctor immediately or go to the casualty department at your nearest hospital:

The following side effects have been reported less frequently:

- swelling of the hands, feet, ankles, face, lips, mouth or throat, which may cause difficulty in swallowing or breathing,
- rash or itching,
- fainting.

These are all very serious side effects. If you have them you may have had a serious allergic reaction

to BIO-PEN. You may need urgent medical attention.

Tell your doctor immediately if you notice any of the following:

The following side effects have been reported frequently:

- Jarisch-Herxheimer reaction in patients treated for syphilis which may manifest as fever, chills, headache and reactions at the site of the lesion, low blood pressure, increased heart rate and flushing,
- allergic reactions including exfoliative dermatitis (large scaly skin inflammation), skin rashes inflammation of the blood vessels, fever and joint pain or stiffness,
- a generalised sensitivity reaction with wheels (urticaria), fever, joint pains and increased white blood cells can develop within a few hours to several weeks after starting treatment,
- yellowing of the skin and eyes (jaundice).

The following side effects have been reported less frequently:

- blood disorders e.g. decreased red blood cells, white blood cells and platelets or all of them,
- an acute condition involving a severe and dangerous lowered white blood cell count causing increased vulnerability to infection,
- blood-clotting disorders,
- skin rash with fever and blisters called erythema multiforme,
- severe allergic reactions affecting the whole body or which causes difficulty in breathing, such as asthma, skin bleeding, stomach and bowel disorders,
- if you have a skin fungal infection, you might experience allergic reactions because your body confuses penicillin with the fungus, because the fungus and penicillin have similar components that your immune system reacts to,

- nerve disorders, seizures, especially when patients received very high doses of BIO-PEN or have kidney problems, epilepsy, inflammation of meninges or accumulation of fluid in the brain. This also applies to patients where a machine temporarily takes over the function of the heart and lungs during surgery,
- increases in liver enzymes,
- inflammation of the kidneys.

The following side effects have been reported with unknown frequency:

- superinfection caused by penicillin resistant microorganisms (e.g. *Pseudomonas* and *Candida*),
- chest pain in the context of allergic reactions, which may be a symptom of allergy triggered cardiac infarction (Kounis syndrome).
- reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flulike symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis),
- rash, fever, swollen lymph nodes, and affect internal organs like the liver and kidneys (DRESS).

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following:

Frequent side effects:

- diarrhoea,
- feeling sick (nausea),
- heartburn,
- effect on urine or blood laboratory tests.

Less frequent side effects:

- electrolyte disturbances due to rapid infusion of high doses,
- sore mouth or tongue,
- a black hairy tongue, vomiting,
- kidney disease,
- abnormal presence of the protein albumin or blood in the urine,
- sediment in the urine called cylindruria,
- reduced urine output or failure to excrete urine (this mostly clears up within 48 hours after stopping treatment),
- severe local reactions during administration into a muscle in infants.

Side effects with unknown frequency:

- blood clotting takes longer,
- swelling under the skin, often around the eyes and lips, usually due to an allergic reaction
- metabolic encephalopathy (neurological disorders with convulsions and loss of consciousness),
- skin disease with blisters called pemphigoid,
- AGEP – acute generalised exanthematous pustulosis with symptoms such as severe drug skin reactions with or without reddening of the skin, fever, pustules,
- erythema (inflammatory reddening of the skin),
- rash morbilliform (rash that looks like measles),
- itching, maculo-papular rash (flat and red area on the skin),
- rash with blisters arranged in a circle with central crusting or like a string of pearls (linear IgA disease).

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

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Reporting of side effects

If you get side effects, talk to your doctor, pharmacist or nurse. You can also report side effects to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. By reporting side effects, you can help provide more information on the safety of BIO-PEN.

5. How to store BIO-PEN

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

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

Store all medicines out of reach of children.

Do not use after the expiry date printed on the container.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains and sewerage systems

6. Contents of the pack and other information

What BIO-PEN contains:

The active substance is benzylpenicillin sodium 600 mg (1 million units) or 3 g (5 million units).

The other ingredient is sodium citrate buffer: 4,3 % *w/w*.

What BIO-PEN looks like and contents of the pack

Dry powder: White crystalline powder.

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

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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

Holder of Certificate of Registration

Biotech Laboratories (Pty) Ltd.

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This leaflet was last revised in

04 December 2024.

Registration numbers

BIO-PEN 1 MU – A/20.1.2/444

BIO-PEN 5 MU – A/20.1.2/825