เอกสารกำกับยาภาษาอังกฤษ

POLIZ-B (500,000 UNITS FOR INJECTION)

1. Name of the medicinal product

POLIZ-B (500,000 UNITS FOR INJECTION) 500,000 units powder for solution for infusion

2. Qualitative and quantitative composition

Each vial contains polymyxin B sulfate equivalent to polymyxin B 500,000 units.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Dosage form: Powder for solution for infusion

Product appearance: White to buff-colored sterile lyophilized powder for injection

4. Clinical particulars

4.1 Therapeutic indications

Polymyxin B for injection (polymyxin B sulphate) is used as monotherapy or combination with relevant antibiotics for the treatment of extensively drug-resistant gram negative bacterial infections with limited treatment options, mainly the susceptible strains of *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia*.

Polymyxin B for Injection is indicated for the treatment of patients with the following infections, when caused by susceptible strains of the designated aerobic gram negative bacteria:

- Urinary tract infections caused by *Pseudomonas aeruginosa* and *Escherichia coli*
- Bloodstream infections caused by *Pseudomonas aeruginosa*, *Enterobacter* (formerly called *Aerobacter*) *aerogenes* and *Klebsiella pneumonia*

Polymyxin B for injection should be used where sensitivity suggests more commonly used systemic antibacterial agents may be contraindicated or ineffective because of bacterial resistance.

Polymyxin B for injection should be used only in hospitalized patients under close monitoring for kidney function and neurological signs and symptoms.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of polymyxin B sulphate and other antibacterial drugs, polymyxin B for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4.2 Posology and method of administration

Intravenous (IV):

Loading dose: 20,000 to 25,000 units/kg (2.0 to 2.5 mg/kg), based on total body weight (TBW), infused over 1 hour.

Maintenance dose: 12,500 to 15,000 units/kg (1.25 to 1.5 mg/kg), based on TBW every 12 hours is infused over 1 hour.

Patients with Renal Impairment: Polymyxin B is not significantly eliminated by kidneys and therefore the daily maintenance dose of polymyxin B should not be adjusted.

Patients receiving Renal Replacement Therapy: The loading dose and maintenance dose of polymyxin B should not be adjusted.

Method of administration

Dissolve 500,000 units (50 mg) polymyxin B for injection in 50 to 500 mL of dextrose Injection 5 percent, for continuous IV infusion.

4.3 Contraindications

- Patients who are hypersensitive to polymyxins, including polymyxin B sulphate, or to any component of the container.
- Polymyxin B for injection is contraindicated in patients with myasthenia gravis.

4.4 Special warnings and precautions for use

General

The intravenous administration of polymyxin B for injection should be restricted to hospitalized patients so as to provide constant clinical supervision. The dose greater than the recommendation (see section 4.2) should be avoided in the absence of therapeutic drug monitoring (TDM).

Polymyxin B for injection should be used with extreme caution in patients with porphyria.

Polymyxin B for injection is not active and therefore should not be used for the treatment of bacterial infections caused by gram-negative bacteria (*Proteus* spp., *Providencia* spp., *Morganella* spp., *Serratia marcescens*, *Burkholderia* spp., *Neisseria* spp.), all gram-positive bacteria and anaerobes. It is critical that adjunct therapy be initiated immediately if a concomitant bacterial pathogen is documented or suspected (see section 4.1 and 5.1)

Cardiovascular

QT Interval Prolongation

The effect of polymyxin B for injection on prolonged cardiac repolarization, QT interval, and increased risk of developing cardiac arrhythmia and torsades de pointes is not known.

Gastrointestinal

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with the use of many antibacterial agents, including polymyxin B sulphate. CDAD may range in severity from mild diarrhea to fatal colitis. It

is important to consider this diagnosis in patients who present with diarrhea, symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *C. difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C. difficile*. Surgical evaluation should be instituted as clinically indicated; as surgical intervention may be required in certain severe cases (see section 4.8).

Immune

Hypersensitivity reactions

Serious hypersensitivity reactions including apnea and bronchoconstriction have been reported in patients receiving polymyxin B sulphate by inhalation administration. Anaphylactoid reactions have been reported with parenteral administration of polymyxin B for injection. Patients with a known allergy to bacitracin are at higher risk of developing hypersensitivity reactions with the use of polymyxins as cross-reactivity between bacitracin and polymyxins exists.

Before therapy with polymyxin B for injection is instituted, careful inquiry should be made to determine whether the patient has had a previous hypersensitivity reaction to polymyxins or bacitracin. Polymyxin B for injection should not be administered by inhalation. If an allergic reaction occurs, discontinue the drug. Serious acute hypersensitivity (anaphylaxis or air way constriction) requires emergency treatment as clinically indicated (see section 4.4- Neurologic, Respiratory and section 4.8).

Neurologic

Neurological disturbances including neuromuscular blockade (generalized muscle weakness, respiratory depression or arrest), seizure, circumoral paresthesia or numbness, vertigo, blurred vision, facial flushing, and slurring of speech, have been reported with polymyxin B for injection at therapeutic doses. These usually occur with high serum drug concentrations found in patients with renal impairment, drug nephrotoxicity or with inhalation of polymyxin B sulphate.

Mild neurological manifestations of polymyxins usually subside after prompt cessation of polymyxin B for injection therapy. If signs of respiratory paralysis appear, discontinue use of polymyxin B for injection and other neurotoxic agents immediately. Apnea should be treated with assisted respiration. Avoid concurrent

use of nephrotoxic and/ or neuromuscular blocking curariform muscle relaxants and other potential neurotoxic drugs, which may precipitate respiratory depression (see section 4.4- Renal, Respiratory, section 4.8, section 4.5-Drug-Drug Interactions).

Renal

Polymyxins induce nephrotoxicity by increasing membrane permeability. Rising blood concentrations of polymyxin B, albuminuria, cellular casts, diminishing urine output and rising blood urea nitrogen (BUN) have been reported with the use of polymyxin B for injection at therapeutic doses. Acute renal failure has been reported in patients on polymyxin B for injection therapy. Nephrotoxicity is dose dependent.

Baseline renal function should be assessed prior to and regularly during therapy. In case acute kidney injury (AKI) develops, therapy with polymyxin B for injection should be discontinued immediately if infection diagnosis is uncertain or when an alternative less nephrotoxic drug is available. If AKI develops when polymyxin B is being administered for life-threatening infection or when the infecting pathogen has an MIC higher than 1 mg/L, the polymyxin B dose should not be decreased outside the recommended dose. The nephrotoxic effect is usually reversible upon discontinuation of therapy.

The concurrent use of other nephrotoxic drugs including antimicrobials (particularly bacitracin, aminoglycosides, cephaloridine, cephalothin, amphotericin B, paromomycin, polymyxin E (colistin) and vancomycin) should be avoided (see section 4.5-Drug-Drug Interactions).

Respiratory

Significant deterioration of lung function including apnea, bronchospasm, decreases in vital capacity, forced expiratory volume over one second and maximum voluntary ventilation have been reported following aerosol administration of polymyxin B sulphate. Polymyxin B for injection should not be administered by inhalation (see section 4.8).

Special Populations

Pregnancy

Clinical data from the use of polymyxin B sulphate in pregnant women is not available. Polymyxin B for injection should not be used during pregnancy unless the expected benefit to the mother outweighs any possible risk to the fetus.

Animal studies are also lacking with respect to embryotoxicity and/or teratogenicity of polymyxin B sulphate.

Breast-feeding

It is not known whether polymyxin B sulphate is secreted in breast or animal milk. Because of the potential for unknown effects of the drug in infants being nursed by mothers taking polymyxin B sulphate, a decision should be made to either discontinue nursing or discontinue treatment, taking into account the importance of polymyxin B for injection drug treatment to the mother and the possible risk to the infant.

Geriatrics (≥ 65 years of age)

Limited data is available on the safety and efficacy of polymyxin B sulphate in the elderly. The renal function should be assessed prior to and regularly during therapy.

Monitoring and Laboratory Tests

Renal

Consideration should be given to monitoring renal function (albuminuria, cellular casts, BUN, serum creatinine or creatinine clearance) prior to and regularly during polymyxin B for injection treatment.

Neurologic

Patients should be monitored for neurologic signs and symptoms (e.g., apnea, numbness, vertigo, blurred vision, facial flushing and slurring of speech) during polymyxin B for injection therapy.

Drug-Lab Interactions

Consideration should be given to monitoring electrolyte abnormalities such as hypokalemia, hyponatremia, hypochloremia.

Warnings (based on the Ministry of Public Health's Announcement)

1. Do not use in patients with known hypersensitivity to polymyxins.
2. This drug may be harmful to the kidneys and nervous systems.

4.5 Interaction with other medicinal products and other forms of interaction

Overview

Concomitant administration of diuretics and potential nephrotoxic and/or neurotoxic agents including antimicrobials increases the likelihood of renal toxicity, whereas non-polarizing muscle relaxants and other neurotoxic drugs increase the likelihood of serious neurotoxicity.

Drug-Drug Interactions

The concurrent use of other nephrotoxic and/or neurotoxic drugs particularly bacitracin, kanamycin, streptomycin, tobramycin, amikacin, cephaloridine, cephalothin, paromomycin, polymyxin E (colistin), neomycin, gentamicin, and vancomycin should be avoided (see section 4.4-Neurologic).

Due to the effect of polymyxin B sulphate on the release of acetylcholine, non-polarizing muscle relaxants (ether, tubocurarine, gallamine, decamethonium, sodium citrate), depolarizing muscle relaxant succinylcholine, and other neurotoxic drugs should not be used concurrently with polymyxin B sulphate (see section 4.4-Respiratory).

The concurrent use of polymyxin B for injection with potent diuretics such as ethacrynic acid or furosemide should be avoided, since diuretics may enhance polymyxin B sulphate toxicity by altering the antibiotic concentration in serum and tissues.

Drug-Food Interactions

Information not available.

Drug-Herb Interactions

Information not available.

Drug-Laboratory Interactions

Information not available.

Drug-Lifestyle Interactions

Information not available.

4.6 Fertility, pregnancy and lactation

Pregnancy

Clinical data from the use of polymyxin B sulphate in pregnant women is not available. Polymyxin B for injection should not be used during pregnancy unless the expected benefit to the mother outweighs any possible risk to the fetus.

Animal studies are also lacking with respect to embryotoxicity and/or teratogenicity of polymyxin B sulphate.

Breast-feeding

It is not known whether polymyxin B sulphate is secreted in breast or animal milk. Because of the potential for unknown effects of the drug in infants being nursed by mothers taking polymyxin B sulphate, a decision should be made to either discontinue nursing or discontinue treatment, taking into account the importance of polymyxin B for injection drug treatment to the mother and the possible risk to the infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse drug reaction overview

The most common drug-related adverse reactions are nephrotoxicity and neurotoxicity, pain at the injection site, urticaria, and electrolyte imbalance.

Clinical trial adverse drug reactions

Prospective clinical trials were not conducted for polymyxin B for injection. Therefore drug-related adverse reactions that could occur are derived from adverse drug reporting from retrospective clinical studies.

- Renal and urinary disorders: albuminuria, cylindruria（urinary cast）, azotemia（a diminishing urine output and rising BUN).
- Nervous system disorders: facial flushing, dizziness progressing to ataxia, drowsiness, circumoral, lingual and peripheral paresthesia (stocking-glove distribution）, apnea due to concurrent use of curariform muscle relaxants or other neurotoxic drugs, or inadvertent overdosage.
- General disorders & Administration site conditions: thrombophlebitis at intravenous injection sites.

Less common clinical trial adverse drug reactions (<1%)

Information not available.

Abnormal hematologic and clinical chemistry findings

Electrolyte imbalance (including hyponatremia, hypochloremia and hypocalcemia) has been reported during parenteral therapy in patients with serious underlying malignant disease.

Eosinophilia has been reported, but the significance of this finding is not established.

Post-market adverse drug reactions

- Gastrointestinal Disorders: pseudomembraneous colitis.
- Immune System Disorders: bronchoconstriction following administration of nebulized polymyxins, anaphylactoid reactions, rash/pruritus, dermatitis and drug fever.
- Nervous System Disorders: facial paralysis, partial deafness, visual disturbance, vertigo, seizure and neuromuscular weakness and neuromuscular blockade.
- Renal and Urinary Disorders: acute renal failure.

4.9 Overdose

Polymyxin-induced toxicity associated with overdose has been reported. Overdose of polymyxin can result in neuromuscular blockade, which can lead to apnea, muscular weakness, vertigo, transient facial paresthesia, slurred speech, vasomotor instability, visual disturbance, confusion, psychosis and possible respiratory arrest. Overdose can also cause renal failure characterized by decreased urine output and increased serum concentrations of BUN and creatinine.

There is no specific antidote for polymyxin B sulphate overdose. In case of polymyxin B sulphate overdose, the drug should be stopped and symptomatic treatment instituted.

Quick diuresis by IV administered mannitol may help to enhance renal clearance of the drug and thus to reduce serum drug level. Hemodialysis or peritoneal dialysis may help in order to manage renal complications.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemics use, polymyxins, ATC code: J01XB02

Mechanism of action

The antibiotic lipopeptide polymyxin is a large molecular weight detergent. Polymyxin acts by way of three known mechanisms. Polymyxins interact electrostatistically with the outer membranes of gram-negative bacteria and competitively displace divalent cations from the membrane lipids, specifically calcium and magnesium that stabilize the lipopolysaccharide molecule. This disrupts the outer membrane and releases lipopolysacchrides. The change in the permeability of the bacterial membrane leads to leakage of the cell content and subsequently cell lysis and death. Polymyxins are surface-active amphipathic agents containing both lipophilic and lipophobic groups. They penetrate into cell membranes and interact with phospholipids

in the membranes, leading to permeability changes that quickly disrupt cell membranes and cell death. Polymyxins also bind to the lipid A portion of endotoxin or LPS molecules.

Polymyxins are active for gram-negative bacteria only. *Acinetobacter* spp., *Pseudomonas aeruginosa*, *E coli*, *Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp. (formerly called *Aerobacter*), *Hemophilus influenzae* are commonly susceptible to polymyxins. However, *Proteus* spp, *Providencia* spp, *Morganella* spp., *Serratia* spp., *Burkholderia* spp., *Moraxella* spp., *Neisseria* spp., all gram-positive bacteria and most anaerobes are less active/naturally resistant to polymyxins.

Mechanism(s) of Resistance

Resistance to polymyxins can develop through mutational or adaptive mechanisms, with almost complete cross resistance with other polymyxins. Polymyxin resistance has been reported by various mechanisms; (1) by modification of the phosphate groups of lipopolysacchrides due to substitution with ethanolamine or aminoarabinose; (2) increased production of the outer membrane protein H1.

Naturally resistant gram-negative bacteria such as *Proteus mirabilis* and *Burkholderia cepacia*, show complete substitution of the lipid phosphate by ethanolamine or aminoarabinose.

Cross-Resistance

Complete cross-resistance has been reported with colistin (polymyxin E).

Safety Pharmacology

Data on delayed ventricular repolarization (QT/QTc) and convulsion potential are not available.

Pharmacodynamics

Polymyxins are bactericidal targeting the bacterial cell membrane. The pharmacodynamics of polymyxin B sulphate are concentration dependent. The ratio of the area under the plasma concentration-time curve to the bacterial minimum inhibitory concentration (AUC/MIC) is the most predictive efficacy index.

5.2 Pharmacokinetic properties

Polymyxin B sulphate is not absorbed from the gastrointestinal tract. After intravenous infusion of polymyxin B in critically ill patients, the median human protein binding is 58% (range, 36% – 74%). Low volume of distribution of polymyxin B (approximately 0.09 L/kg) is reported. The biotransformation of the intravenous polymyxin B is incompletely characterized. Polymyxin B is low urinary recovery (median 4.04%; range, 0.98% - 17.4%), suggesting that renal route is not a major pathway of polymyxin B elimination. Half-life of intravenous polymyxin B in critically ill patients is reported to be around 11.9 hours, with a mean total body clearance, scaled by TBW of approximately 0.03 L/h/kg.

Pharmacokinetics in special population

Renal insufficiency

Pharmacokinetic of polymyxin B was evaluated in patients with renal insufficiency (estimated creatinine clearance < 80 mL/min) and patients with normal renal function (estimated creatinine clearance $\geq$ 80

mL/min). The adjusting AUC for daily dose (in IU/kg of TBW) was determined and reported that polymyxin B exposures in patients with normal and impaired renal function after receiving standard dosing of polymyxin B were comparable, suggesting that polymyxin B clearance did not depend on creatinine clearance. Therefore, polymyxin B dose adjustment should not be necessary in patients with impaired renal function (see section 4.2).

5.3 Preclinical safety data

No studies of preclinical safety data have been available.

6. Pharmaceutical particulars

6.1 List of excipients

POLIZ-B (500,000 UNITS FOR INJECTION) does not contain any excipients.

6.2 Incompatibilities

Polymyxin B is inactivated by strong acidic or alkaline solutions. The drug is chemically incompatible with many drugs including amphotericin B, ampicillin sodium, cloxacillin sodium, cefiderocol sulfate tosylate, cefazolin, chloramphenicol sodium succinate, chlorothiazide sodium, and heparin sodium. Polymyxin B in solution is also incompatible with the salts of calcium and magnesium.

6.3 Shelf life

Before reconstitution : The expiry date is indicated on the packaging.

After reconstitution : Store in the refrigerator (2-8°C) for 72 hours or store below 30°C for 3 hours. (see section 6.6)

6.4 Special precautions for storage

Store below 30°C.

Protect from light.

Keep the vial in the outer carton.

6.5 Nature and contents of container

Each glass vial type I contains 500,000 units polymyxin B.

Each box contains 1 vial.

6.6 Special precautions for disposal and other handling

Polymyxin B for injection must be reconstituted before use, using aseptic technique.

The reconstituted solution should be clear. Do not use if particles are present.

Reconstitution for Intravenous Administration

Dissolve 500,000 units (50 mg) polymyxin B for injection (1 vial) in 50 to 500 mL of dextrose Injection 5 percent, for continuous IV drip. Reconstituted solution should be stored under refrigeration (2-8°C) and the unused portion should be discarded after 72 hours or should be stored below 30°C and the unused portion should be discarded after 3 hours.

The reconstituted solutions of POLIZ-B (500,000 UNITS FOR INJECTION) should be used immediately. If not use immediately, the solutions are stable under storage conditions which are mentions in section 6.3.
For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Manufacturer :-

Siam Bheasach Co., Ltd.

123 Soi Chokechai Ruammitr, Vibhavadi-Rangsit Rd., Chomphon, Chatuchak, Bangkok 10900, Thailand.
and 9 Soi Chokechai Ruammitr 3, Vibhavadi-Rangsit Rd., Dindang, Dindang, Bangkok 10400, Thailand.

Distributor :-

Siam Pharmaceutical Co., Ltd.

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Tel. 02-6259999

8. Marketing authorisation number(s) :- 1A 114/67

9. Date of first authorisation/renewal of the authorization :- (06/11/2024)

10. Date of revision of the text :- (06/11/2024)