

PRODUCT MONOGRAPH

Pr POLYMYXIN B FOR INJECTION USP

Powder for Solution
Polymyxin B, 50 mg/vial (500,000 units)
(as polymyxin B sulphate)

Antibiotic

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Date of Preparation:
November 9, 2011

Submission Control No: 143565

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P^rPOLYMYXIN B FOR INJECTION USP

(as Polymyxin B Sulphate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous, Intramuscular, Intrathecal, Ophthalmic (topical and subconjunctivally)	Powder for solution, polymyxin B, 50 mg/vial (500,000 units) (as polymyxin B sulphate)	Not applicable

INDICATIONS AND CLINICAL USE

Polymyxin B for Injection USP (polymyxin B sulphate) 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*
- **Meningeal infections** caused by *Pseudomonas aeruginosa*
- **Corneal and subconjunctival eye infections** caused by *Pseudomonas aeruginosa*

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, if prescribed for intravenous, intramuscular or intrathecal administration, 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 sulphate 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.

CONTRAINDICATIONS

- Patients who are hypersensitive to polymyxins, including polymyxin B sulphate, or to any component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Polymyxin B for Injection USP is contraindicated in patients with myasthenia gravis.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Polymyxin B for Injection USP is nephrotoxic therefore renal function should be assessed prior to and regularly during treatment. Dose adjustment is required in patients with reduced renal function (See **WARNINGS AND PRECAUTIONS, Renal, Monitoring and Laboratory Tests, Renal; ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION**).
- Polymyxin B for Injection USP at therapeutic doses may cause serious neurotoxic symptoms as manifested by ataxia, seizure and neuromuscular blockade. These are usually associated with high drug serum levels found in patients with impaired renal function and/or nephrotoxicity (See **WARNINGS AND PRECAUTIONS, Neurologic, Respiratory; Monitoring and Laboratory Tests, Neurologic; ADVERSE REACTIONS**).
- The concurrent/sequential use of other nephrotoxic drugs including antimicrobials should be avoided with Polymyxin B for Injection USP treatment (See **WARNINGS AND PRECAUTIONS, Neurologic, Renal; Monitoring and Laboratory Tests, Renal, DRUG INTERACTIONS, Drug-Drug Interactions**).
- The concurrent/sequential use of anaesthetic and other neurotoxic drugs should be avoided with Polymyxin B for Injection USP treatment. The neurotoxicity of polymyxin B sulphate can result in respiratory paralysis from neuromuscular blockade, especially when the drug is given soon after anaesthesia and/or muscle relaxants. If signs of respiratory paralysis appear, assist respiration and withdraw the drug (See **WARNINGS AND PRECAUTIONS, Immune, Neurologic, Renal, Respiratory; Monitoring and Laboratory Tests, Renal, Neurologic; DRUG INTERACTIONS, Drug-Drug Interactions**).

General

The intramuscular, intravenous, and/or intrathecal administration of Polymyxin B for Injection USP should be restricted to hospitalized patients so as to provide constant clinical supervision. Maximum dosage should not exceed 2.5 mg/kg/day or a total of 200 mg/day in patients with normal renal function.

Intramuscular dosage is not recommended routinely because of severe pain at injection sites. When procaine is used with polymyxin B sulphate to lessen the pain of intramuscular injection, care should be taken not to give; intrathecally or intravenously, solutions that have been prepared with procaine for intramuscular use (See **DOSAGE AND ADMINISTRATION**).

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

Polymyxin B sulphate 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 **INDICATIONS AND CLINICAL USE; ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action, PART II: SCIENTIFIC INFORMATION, MICROBIOLOGY**).

Cardiovascular

QT Interval Prolongation

The effect of polymyxin B sulphate 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 **ADVERSE REACTIONS**).

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 sulphate. 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 USP 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 USP 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 **WARNINGS AND PRECAUTIONS, Neurologic, Respiratory, ADVERSE REACTIONS**).

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 sulphate 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 sulphate therapy. If signs of respiratory paralysis appear, discontinue use of polymyxin B sulphate 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 **WARNINGS AND PRECAUTIONS: Renal, Respiratory; ADVERSE REACTIONS, DRUG INTERACTIONS, Drug-drug Interactions; Monitoring and Laboratory Tests, Neurologic**).

Ophthalmic

Subconjunctival administration of polymyxin B sulphate may be painful. Deep seated or walled off *Pseudomonas aeruginosa* infections cannot be expected to respond to ophthalmic treatment and may require systemic therapy. Therefore, Polymyxin B for Injection USP should not be used for treatment of these infections.

Renal

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

Baseline renal function should be assessed prior to and regularly during therapy. Since elderly patients may have impaired renal function, special care should be taken with drug dosing. If renal dysfunction develops, therapy with polymyxin B sulphate should be discontinued immediately. The nephrotoxic effect is usually reversible upon discontinuation of therapy.

In patients with pre-existing renal dysfunction, polymyxin B sulphate dosage adjustment and frequent renal function assessment are required because of the potential for increased drug accumulation under these conditions (See **ADVERSE REACTIONS: DRUG INTERACTIONS: Drug-drug Interactions; DOSAGE AND ADMINISTRATION, Patients with Renal Impairment**).

The concurrent use of other nephrotoxic drugs including antimicrobials (particularly bacitracin, aminoglycosides, cephaloridine, cephalothin, amphotericin B, paromycin, polymyxin E (colistin) and vancomycin) should be avoided (See **DRUG INTERACTIONS, Drug-Drug Interactions; Monitoring and Laboratory Tests, Renal**).

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 USP should not be administered by inhalation (See **ADVERSE REACTIONS; DOSAGE AND ADMINISTRATION**).

Special Populations

Pregnant Women

Clinical data from the use of polymyxin B sulphate in pregnant women is not available. Polymyxin B for Injection USP 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.

Nursing Women

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 USP drug treatment to the mother and the possible risk to the infant.

Pediatrics (<18 years)

Safety and efficacy of polymyxin B sulphate in children greater than 2 years of age is limited. Renal function should be frequently monitored in this population.

Safety and efficacy of parenteral polymyxin B sulphate in infants less than 2 years of age is limited. A possibility of higher serum levels and prolonged half-life has been reported in infants and neonates, therefore dosage recommendations are not available in this population (See **DOSAGE AND ADMINISTRATION; PART II: SCIENTIFIC INFORMATION, DETAILED PHARMACOLOGY**).

Geriatrics (≥ 65 years of age)

Limited data is available on the safety and efficacy of polymyxin B sulphate in the elderly. The decline in renal function with advanced age should be considered and 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, blood urea nitrogen (BUN), serum creatinine or creatinine clearance) prior to and regularly during Polymyxin B for Injection USP 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 USP therapy.

Drug-Lab Interactions:

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

ADVERSE REACTIONS

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 sulphate. 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, signs of meningeal irritation presenting as convulsions and signs of meningismus with intrathecal administration (e.g., fever, headache, seizure, stiff neck and increased cell count and protein in cerebrospinal fluid following intrathecal/intraventricular administration of polymyxin B sulphate).

Immune System Disorders: urticarial rash at intramuscular injection sites. Allergic hypersensitivity following topical application of polymyxin B sulphate has been reported.

General Disorders & Administration Site Conditions: pain (severe) at intramuscular injection sites, and 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

Eye Disorder: ophthalmic application of polymyxin B sulphate has reported low-grade conjunctivitis

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

DRUG INTERACTIONS

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, paromycin, polymyxin E (colistin), neomycin, gentamicin, and vancomycin should be avoided (See **WARNINGS AND PRECAUTIONS - 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 **WARNINGS AND PRECAUTIONS, Respiratory**).

The concurrent use of polymyxin B sulphate 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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Polymyxin B for Injection USP may be administered intravenously, intramuscularly or intrathecally only to hospitalized patients under constant supervision by a physician. Dosage should not exceed 2.5 mg/kg/day or 200 mg/day. Larger doses may produce nephrotoxicity. Transient neurotoxic symptoms may be seen with therapeutic doses.

Estimation of renal function prior to and regularly during therapy is recommended. Monitoring of renal function is strongly recommended in the elderly and in patients with renal impaired function.

Subconjunctival injection of polymyxin B sulphate is painful.

Polymyxin B for Injection USP should not be administered by inhalation.

In medical literature, dosages have been given in terms of equivalent weights of pure polymyxin B base. Each milligram of pure polymyxin B is equivalent to 10,000 units of polymyxin B.

Safety and efficacy of polymyxin B sulphate in children greater than 2 years is limited. Renal function should be frequently monitored in this population.

Safety and efficacy of intravenous and intramuscular polymyxin B sulphate administration in infants less than 2 years of age is limited. A possibility of higher serum levels and prolonged half-life has been reported in infants and neonates, therefore dosage recommendations are not available for this population (See **PART II: SCIENTIFIC INFORMATION, DETAILED PHARMACOLOGY**).

Recommended Dose and Dosage Adjustment

Intravenous:

Adults and Children (Older than 2 years): A total of 1.5 to 2.5 mg/kg/day in individuals with normal kidney function. The total daily dose must not exceed 2.5 mg/kg/day or in any case, 200 mg/day.

Elderly (≥ 65 years): Renal status of elderly patients may be impaired, therefore renal function assessment prior to and regularly during treatment is suggested to provide guidance for dosing in

such patients.

Patients with Renal Impairment: Polymyxin B sulphate is eliminated primarily by the kidney and therefore the dosage should be reduced from 1.5 mg/kg for individuals with kidney impairment. No dosing recommendations in patients on peritoneal dialysis- or hemodialysis are available (See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics; DETAILED PHARMACOLOGY, Pharmacokinetics, Factors Influencing Pharmacokinetics, Special Populations, Renal Insufficiency**).

Reconstitution for Intravenous Administration

Dissolve 50 mg polymyxin B sulphate powder in 200 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 24 hours.

Administration

Infusions may be given every 12 or 8 hours over a period of approximately 60 to 90 minutes.

Intramuscular:

Adults and Children (older than 2 years): 1.5 to 2.5 mg/kg/day in individuals with normal kidney function. Dosage may be divided and given at either 4 or 6 hour intervals.

Elderly (≥ 65 years): Renal status of elderly patients may be impaired, therefore renal function assessment prior to and regularly during treatment is suggested to provide guidance for dosing in such patients.

Patients with Renal Impairment: The dosage should be reduced in individuals with kidney impairment. No dosing recommendations in patients on peritoneal dialysis or hemodialysis are available (See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics; DETAILED PHARMACOLOGY, Pharmacokinetics, Factors Influencing Pharmacokinetics, Special Populations, Renal Insufficiency**).

Reconstitution for Intramuscular Administration

Polymyxin B for Injection USP is compatible with the following reconstitution diluents for intramuscular administration:

- Sterile Water for Injection
- Sodium Chloride Injection 0.9 percent
- Procaine hydrochloride Injection 1 percent or 2 percent.

To the vial containing Polymyxin B for Injection USP 50 mg, add diluent volume as shown in Table 1. Shake well to dissolve the powder.

Table 1: Reconstitution of Polymyxin B for Injection USP for 4 Hour Intramuscular Administration in Adults and Children (older than 2 years)					
Patient Population	Total Average Daily Dose	Polymyxin B sulphate per vial	Volume of Diluent to be Added	Nominal Concentration Per mL	Dose Volume per 4 Hours
80 kg or more	Up to 200 mg	50 mg	3 mL	16 mg/mL	2 mL
60 to 80 kg	150 mg	50 mg	4 mL	12.5 mg/mL	2 mL
40 to 60 kg	100 mg	50 mg	6 mL	8 mg/mL	2 mL
20 to 40 kg	50 mg	50 mg	6 mL	8 mg/mL	1 mL
Less than 20 kg	1.5 - 2.5 mg/kg/day	50 mg	6 mL	8 mg/mL	As calculated

Reconstituted solutions should be stored under refrigeration (2-8°C) and the unused portion should be discarded after 24 hours.

Note:

Dibucaine hydrochloride can potentiate the neurotoxic effects of polymyxins and should not be used as a diluent for IM injection.

Administration

Intramuscular administration is not recommended routinely because of severe pain at injection sites, particularly in children. Pain may be immediate or delayed. The immediate type may be prevented by the presence of a local anaesthetic in the drug solution. The delayed type tends to develop about 1 hour after injection and is not prevented by the presence of a local anaesthetic.

Polymyxin B for Injection USP should be injected well within the body of a relatively large muscle such as in the upper outer quadrant of the buttock or the lateral thigh. To avoid the possibility of radial nerve injury, injections should not be made into the lower and middle thirds of the upper arm. Aspiration and proper anatomical selection of injection site should be observed as a precaution against inadvertent injection into a blood vessel or a major nerve.

Intrathecal:

Adults and Children (older than 2 years): Dosage is 5 mg once daily intrathecally for 3 or 4 days, then 5 mg once every other day for at least 2 weeks after cultures of the cerebrospinal fluid are negative and sugar content has returned to normal.

Infants (less than 2 years): 2 mg once daily intrathecally for 3 to 4 days or 2.5 mg once every other day. Continue with a dose of 2.5 mg once every other day for at least 2 weeks after cultures of the cerebrospinal fluid are negative and sugar content has returned to normal.

Reconstitution for Intrathecal Administration

Dissolve 50 mg Polymyxin B for Injection USP in 10 mL Sodium Chloride Injection 0.9 percent to obtain a concentration of 5 mg/mL polymyxin B sulphate. Shake well. Reconstituted solutions should be stored under refrigeration (2-8°C) and the unused portion should be discarded after 24 hours.

Administration

Adults and Children (older than 2 years): Inject 1 mL (5 mg) of reconstituted polymyxin B sulphate solution intrathecally.

Infants (less than 2 years): Inject 0.4 mL (2 mg) of reconstituted polymyxin B sulphate solution intrathecally for 3 to 4 days or 0.5 mL (2.5 mg) once every other day.

Ophthalmic:

Topical

1 to 2.5 mg/mL (0.1 to 0.25 percent w/v) solution as 1 to 3 drops every hour, increasing the interval as response indicates.

Deep seated or walled off *Pseudomonas aeruginosa* infections cannot be expected to respond to topical polymyxin B treatment.

Reconstitution for Topical Administration

Dissolve 50 mg Polymyxin B for Injection USP powder in 20 to 50 mL of Sterile Water for Injection USP or Sodium Chloride Injection USP 0.9 percent, for 1 to 2.5 mg/mL concentration. Reconstituted solutions should be stored under refrigeration (2-8°C) and the unused portion should be discarded after 72 hours.

Administration

Instill 1 to 3 drops in the affected eye every hour, increasing the interval as response indicates.

Subconjunctival

Subconjunctival injection of up to 1 mg/day is administered for the treatment of *Pseudomonas aeruginosa* infections of the cornea and conjunctiva.

Reconstitution for Subconjunctival Administration

Dissolve 50 mg polymyxin B sulfate lyophilized powder in 50 mL of Sterile Water for Injection USP or Sodium Chloride Injection USP for a 1 mg/mL concentration. Reconstituted solutions should be stored under refrigeration (2-8°C) and the unused portion should be discarded after 24 hours.

Administration

1 mL of reconstituted polymyxin B sulphate solution.

Avoid total systemic and ophthalmic instillation over 2.5 mg/kg/day.

Missed Dose

This information is not available.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 levels. Hemodialysis or peritoneal dialysis may help in order to manage renal complications.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The antibiotic lipopeptide polymyxin is a large molecular weight detergent. Polymyxin acts by way of three known mechanisms. Polymyxins interact electrostatically 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 lipopolysaccharides. 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.

Pharmacokinetics:

Polymyxin B sulphate is not absorbed from the gastrointestinal tract. Serum polymyxin B sulphate concentrations are low because 79% to 92% of the drug loses its activity due to protein binding. The drug is excreted primarily by the kidneys. After an initial dose of polymyxin B sulphate there is a 12 to 24 hour lag period before significant amounts of drug are found in urine. Less than 1% of infused polymyxin B sulphate is recovered in the urine. At therapeutic dosages, polymyxin B sulphate has been reported to cause nephrotoxicity as shown by slight tubular damage.

Pharmacokinetic parameters of polymyxin B sulphate are shown in Table 2 below:

Table 2 – Pharmacokinetic Parameters for Polymyxin B Sulphate^a	
	Polymyxin B Sulphate
C _{max}	8 mg/L
Time to C _{max}	2h
Half-life	6h
Half-life with renal insufficiency	48-72 h
Elimination	60% recovered in urine
Volume of distribution	ND

^a Following a 50 mg intramuscular dose of polymyxin B sulphate
 ND = Not Determined

Polymyxins are not effectively removed by hemodialysis and the effect of high-flux dialyzers is unknown. No information concerning the removal of polymyxin B sulphate by peritoneal dialysis is available.

Special Populations and Conditions

Pediatrics: The limited data available on the use of polymyxins in children suggests that the pharmacokinetics are similar in children and adults. The limited data available on the use of polymyxin B sulphate in neonates suggests a possibility of higher peak serum levels and prolonged half-life in infants and neonates (See **DETAILED PHARMACOLOGY**).

Renal Insufficiency: Patients with impaired renal function demonstrated an increased accumulation of polymyxin B sulphate. Pharmacokinetic data in patients with renal insufficiency are scarce, therefore no definite dosing recommendations can be made in these patients (See **DETAILED PHARMACOLOGY**).

No data is available on the use of polymyxin B sulphate in patients receiving peritoneal dialysis. Polymyxins are not effectively removed by hemodialysis.

STORAGE AND STABILITY

Before reconstitution: Store at room temperature (15-30°C). Protect from light. Retain in carton until time of use.

After reconstitution for Intravenous, Intramuscular, Intrathecal and Ophthalmic (Subconjunctival):

Reconstituted solutions should be stored under refrigeration (2-8°C) and the unused portion should be discarded after 24 hours.

After reconstitution for Ophthalmic (Topical): Reconstituted solutions should be stored under refrigeration (2-8°C). Any unused portion should be discarded after 72 hours.

Polymyxin B sulphate should not be stored in alkaline solutions since they are less stable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Polymyxin B for Injection USP is available as a powder for solution. It is available in single vial cartons containing 50 mg/vial (500,000 units) as polymyxin B sulphate.

Polymyxin B for Injection USP powder for solution does not contain any non-medical ingredients.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

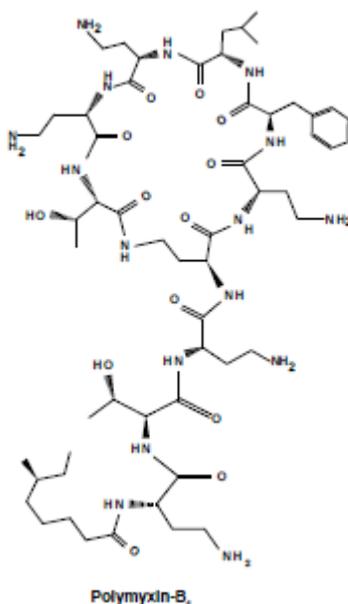
Proper name: Polymyxin B Sulphate

Chemical name: N-[4-amino-1-[[[1-[[4-amino-1-oxo-1-[[6,9,18-tris(2-aminoethyl)-15-benzyl-3-(1-hydroxyethyl)-12-(2-methylpropyl)-2,5,8,11,14,17,20-hepta-oxo-1,4,7,10,13,16,19-heptazacyclotricos-21-yl]amino]butan-2-yl]amino]-3-hydroxy-1-oxobutan-2-yl]amino]-1-oxobutan-2-yl]-6-methyloctanamide; sulfuric acid

Molecular formula: $C_{56}H_{98}N_{16}O_{13} \cdot 2.5 (H_2SO_4)$

Molecular mass: 1449 g/mol

Structural formula:



Physicochemical properties: Polymyxin B sulphate is a white or almost white, almost odourless, hygroscopic powder. Polymyxin B sulphate is soluble in water and slightly soluble in alcohol. A 0.5% solution in water has pH 5.0 - 7.5 (USP) and a 2% solution has pH 5.0 - 7.0 (Ph.Eur.).

CLINICAL TRIALS

Data from original clinical studies are no longer available.

DETAILED PHARMACOLOGY

Safety Pharmacology

Safety pharmacology studies on delayed ventricular repolarization (QT/QTc), respiratory and central nervous system are not available.

Pharmacokinetic/Pharmacodynamic Parameters

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.

Pharmacokinetics

Polymyxin B sulphate is not absorbed from the gastrointestinal tract. Serum polymyxin B sulphate concentrations are low because 79% to 92% of the drug loses its activity due to protein binding. The drug is excreted primarily by the kidneys. Tissue diffusion is poor and the drug does not penetrate well into cerebrospinal fluid, pleural fluid or joints.

At therapeutic dosages, polymyxin B sulphate has been reported to cause nephrotoxicity as shown by slight tubular damage.

Following a 50 mg intramuscular dose, a peak concentration of 8 µg/mL was achieved in approximately 2 hours and serum half life was approximately 6 hours. Following multiple 2-4 mg/kg/day intramuscular polymyxin B sulphate, in divided doses, blood serum levels were reported to be 1-8 µg/mL. The peak levels occurred within 30 minutes to 2 hours after injection, the half-life was about 4.5 to 6 hours and the drug remained detected up to 12 hours. When Polymyxin B sulphate was given at a dose of 2.5 mg/kg/day for 7 days, drug accumulation was reported and peak serum concentrations reached 15-30 µg/mL.

The primary route of polymyxin B sulphate excretion is via the kidney. After an initial dose of polymyxin B sulphate there was a 12 to 24 hour lag period with only a small amount of drug (<1%) being recovered in the first 12 hours after injection. As therapy continues, the urinary concentration increases and eventually 60% of the dose can be accounted for in the urine and urinary concentrations of 10 to 100 µg/mL are attained. The fate of the remaining 40% was unclear, as polymyxins are not excreted in bile.

Factors Influencing Pharmacokinetics

Special Populations

Pediatrics (≤ 18 years)

The limited data available on the use of polymyxin B sulphate in children suggests that the pharmacokinetics are similar in children (> 2 years) and adults. The limited data available on the use of polymyxin B sulphate in infants (< 2 years) suggests a possibility of higher peak serum levels and prolonged half-life in infants and neonates.

Plasma and urine levels 1 hour following a single intramuscular dose of 0.8 mg/kg in children (n=6) demonstrated considerable drug level variation, i.e., 0.4 - 19.0 (average 8.6) µg/mL and 0.2 - 48.0 (average 19.5) µg/mL in plasma and urine respectively, however these drug levels decreased to 0.6 - 9.2 (average 3.8) µg/mL and < 0.2 µg/mL in plasma and urine, respectively, after 4 hours of polymyxin B sulphate administration.

Renal Insufficiency

Patients with renal dysfunction demonstrated an increased accumulation of polymyxin B sulphate. When a dose of 20 mg of polymyxin B was given intramuscularly every 8 hours, patients with renal dysfunction maintained serum levels at 2-5 µg/mL. Following a 50 mg dose, the serum half-life of approximately 6 hours reported in patients with normal kidney function increased to 2-3 days in patients who were anuric.

Polymyxins are not effectively removed by hemodialysis and the effect of high-flux dialyzers is unknown. No information concerning the removal of polymyxin B sulphate by peritoneal dialysis is available.

Critically ill patients with renal impairment report lower than effective plasma concentrations after a few doses and frequently even at steady state. Based upon these findings, a higher first loading dose has been suggested.

MICROBIOLOGY

Polymyxin B sulphate is isolated from *Bacillus polymyxa*. Polymyxins are rapidly bactericidal and target the bacterial cell membrane.

Mode of Action

Lipopeptide polymyxins (polymyxin B/colistin) are surface active amphipathic agents, which interact strongly with phospholipids within the cell membrane and act in a detergent-like fashion to disrupt the structure of the cell membrane. The initial association of the polymyxin B/colistin with the bacterial membrane occurs through interactions between the cationic polypeptide (polymyxin B/colistin) and the anionic lipopolysaccharide within the outer membrane of the gram-negative bacteria, leading to derangement of cell membrane. Polymyxin displaces magnesium and calcium (ions that normally stabilize the lipopolysaccharide molecules) from the negatively charged lipopolysaccharide, leading to a loss of integrity of the membrane, an increase in the permeability of the cell envelope, leakage of cell contents, and subsequently, cell death. Polymyxins also avidly bind to the lipid A portion of the endotoxin in the outer membrane of gram-negative bacteria and inactivate the molecule.

Mechanism of Resistance

Resistance to polymyxins can develop through adaptive or mutational mechanisms. Isolates with intrinsic resistance to polymyxins have alterations in lipid A that account for reduced binding. Acquired resistance to polymyxins has been reported in *Escherichia coli* and *Salmonella* spp. by substitution of phosphate groups in lipopolysaccharides.

Esterification of the lipid A moieties 4'-phosphate (with 4-amino-4-deoxy-L-arabinopyronase) and the glycosidic diphosphate (with 2-aminoethanol) results in a decrease in anionic charges. The change in surface charge can cause a decrease in polymyxin B binding site. For *Klebsiella pneumoniae*, lipopolysaccharide-related phosphate substitution with 4-amino-4-deoxy-L-arabinopyronase has also been linked to polymyxin resistance. The development of resistance in *Pseudomonas aeruginosa* is due to increased production of the outer membrane protein H1.

Cross-Resistance

Complete cross-resistance to other polymyxins including colistin has been reported.

Spectrum of Activity

Polymyxins are active for gram-negative bacteria only. Polymyxin B sulphate has been shown to be active against most strains of the following gram-negative bacteria both *in vitro* and in clinical infections as described in the **INDICATIONS AND CLINICAL USE** section. Table 3 contains information on the *in vitro* activity of clinical isolates from surveillance studies.

Table 3. *In vitro* activity of polymyxin B sulphate against gram-negative bacteria for which the clinical efficacy of polymyxin B sulphate has been demonstrated

Organism / Pathogen	Number of clinical isolates	MIC ($\mu\text{g/mL}$)			% susceptible
		Range	50%	90%	
<i>Pseudomonas aeruginosa</i>	8705	$\leq 1 \rightarrow 8$	≤ 1	2	98.7
<i>Enterobacter</i> spp.	4693	$\leq 1 \rightarrow 8$	≤ 1	> 8	83.3
<i>Escherichia coli</i>	18325	$\leq 1 \rightarrow 8$	≤ 1	≤ 1	99.5
<i>Klebsiella</i> spp.	8188	$\leq 1 \rightarrow 8$	≤ 1	≤ 1	98.2

Clinical isolates collected from Asia-Pacific region, Europe, Latin America and North America, 2001-2004.

Table 4 contains information on the *in vitro* activity of clinical isolates from surveillance studies. However clinical significance of these bacterial isolates is unknown.

Table 4. *In vitro* activity of polymyxin B sulphate against organisms for which the clinical efficacy of polymyxin B sulphate has not been established

Organism / Pathogen	Number of clinical isolates	MIC ($\mu\text{g/mL}$)			% susceptible
		Range	50%	90%	
<i>Acinetobacter</i> spp.	2621	$\leq 1 \rightarrow 8$	≤ 1	2	97.9
<i>Aeromonas</i> spp.	368	$\leq 1 \rightarrow 8$	≤ 1	> 8	71.7
<i>Alcaligenes</i> spp.	121	$\leq 1 \rightarrow 8$	2	> 8	63.6

Table 4. *In vitro* activity of polymyxin B sulphate against organisms for which the clinical efficacy of polymyxin B sulphate has not been established

Organism / Pathogen	Number of clinical isolates	MIC ($\mu\text{g}/\text{mL}$)			% susceptible
		Range	50%	90%	
<i>Burkholderia cepacia</i>	153	0.5->8	>8	>8	11.8
<i>Pseudomonas</i> spp. (non <i>aeruginosa</i>)	282	≤ 1 ->8	≤ 1	2	98.7
<i>Stenotrophomonas maltophilia</i>	1256	≤ 0.12 ->8	1	8	72.4
<i>Citrobacter</i> spp	895	≤ 1 ->8	≤ 1	≤ 1	99.1
<i>Proteus</i> spp.	895	≤ 1 ->8	>8	>8	1.3
<i>Proteus mirabilis</i>	1931	≤ 1 ->8	>8	>8	0.7
<i>Salmonella</i> spp.	2909	≤ 1 ->8	≤ 1	4	76.0
<i>Shigella</i> spp.	828	≤ 1 ->8	≤ 1	≤ 1	99.0
<i>Serratia</i> spp.	1919	0.25->8	>8	>8	5.4

Clinical isolates collected from Asia-Pacific region, Europe, Latin America and North America, 2001-2004.

Susceptibility Test Methods

Cation concentrations have been known to affect the activity of polymyxins.

Dilution Techniques

Quantitative methods are used to determine antibacterial minimum inhibitory concentrations (MIC). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. Standardized procedures are based on the dilution method (broth or agar) or equivalent using standardized inoculums and concentrations of polymyxin B sulphate. The MIC values should be interpreted according to the criteria provided in Table 5.

Table 5: Susceptibility Interpretive Criteria

Pathogen	Minimum Inhibitory Concentration ^b		
	S	I	R
PA	≤ 2	4	≥ 8
<i>Acinetobacter</i> spp	≤ 2	-	≥ 4

^b S = Susceptible, I = Intermediate, R = Resistant

Please note discrepancies in susceptibility criteria from various guidance documents as the clinical outcome of patients infected with above-mentioned gram-negative organisms with MIC of 4 $\mu\text{g}/\text{ml}$ is not available. Studies suggest that peak serum conc. after repeated dosing can reach 15 $\mu\text{g}/\text{ml}$. More clinical data is needed to define optimal susceptibility breakpoints.

A report of susceptible (S) indicates that polymyxin B sulphate is likely to inhibit the growth of the pathogen if polymyxin B sulphate in the blood reaches the concentrations usually achievable. A report of intermediate (I) indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is

physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of resistant (**R**) indicates that polymyxin B sulphate is not likely to inhibit the growth of the pathogen if polymyxin B sulphate in the blood reaches the concentrations usually achievable and other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of quality control microorganisms to control the technical aspects of the test procedures. Standard polymyxin B sulphate powder should provide the MIC values noted in Table 6.

Table 6: Acceptable Quality Control Ranges for Susceptibility Testing

QC Organisms	Minimum Inhibitory Concentrations (µg/mL)
<i>Escherichia coli</i> ATCC 25922	0.25-2
<i>Pseudomonas aeruginosa</i> ATCC 27853	1-4

TOXICOLOGY

Information not available.

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- 3) Chen LF and Kaye D. Current Use for Old Antibacterial Agents: Polymyxins, Rifamycins, and Aminoglycosides. *Infect Dis Clin N Am* 2009; 23: 1053-1075.
- 4) Evans ME, Feola DJ, and Rapp RP. Polymyxin B Sulfate and Colistin: Old antibiotics for Emerging Multiresistant Gram-Negative Bacteria. *The Annals of Pharmacotherapy*. 1999; 33: 960-967.
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- 9) Landman D, Georgescu C, Martin DA and Quale J. Polymyxins Revisited. *Clin. Microbiology Reviews* 2008; 21(3): 449-465.

PART III: CONSUMER INFORMATION**^{Pr}Polymyxin B for Injection USP**

This leaflet is part III of a three-part "Product Monograph" published when Polymyxin B for Injection USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Polymyxin B for Injection USP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

- Polymyxin B for Injection USP is used in the treatment of serious infections caused by "gram-negative" bacteria such as *Pseudomonas aeruginosa*.

What it does:

Polymyxin B for Injection USP works to reduce the bacteria that cause serious infections by weakening the cell membrane of the harmful bacteria.

When it should not be used:

Polymyxin B for Injection USP should not be used if:

- you have or have had an allergic reaction to polymyxin B or other polymyxins
- you have myasthenia gravis

What the medicinal ingredient is:

Polymyxin B Sulphate

What the important nonmedicinal ingredients are:

There are no additional ingredients in Polymyxin B for Injection USP.

What dosage forms it comes in:

Polymyxin B for Injection USP is available as powder for solution. It is available in single vial cartons containing polymyxin B 50 mg/vial (500,000 units) as polymyxin B sulphate

WARNINGS AND PRECAUTIONS

- Polymyxin B can be harmful to the kidney, so your doctor will determine whether this drug is suitable for you if you have kidney problems
- Polymyxin B can be harmful to the brain and nervous system and may cause seizures, movement coordination problems (e.g. ataxia) especially in those with kidney problems, so tell your doctor if you have kidney problems
- Avoid use of other drugs that may be harmful to kidneys such as some antibiotics

- Avoid using anesthetics and muscle relaxants at the same time as polymyxin B sulphate as this can slow and stop breathing

Where injection of Polymyxin B for Injection USP into the body is required it should be restricted to hospitalized patients where adequate laboratory control facilities are available, and constant supervision of the patient is possible.

Before you use Polymyxin B for Injection USP talk to your doctor or pharmacist if:

- You have a kidney disease.
- Are pregnant or planning to get pregnant.
- You are taking any prescription medications, over the counter medications or herbal/natural products or remedies.
- You have a prior allergy to a medication.
- You have porphyria (disease of pigment metabolism to the body).

If you develop severe or persistent diarrhea, this may be a sign of a more serious condition and you should contact a doctor immediately.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicine you can buy without a prescription, and natural health products.

Drugs that may interact with Polymyxin B for Injection USP, and should not be used, include:

bacitracin, kanamycin, streptomycin, tobramycin, amikacin, cephaloridine, paromycin, polymyxin E (colistin), neomycin, gentamicin, vancomycin, tubocurarine, succinylcholine, gallamine, decamethonium and sodium citrate

PROPER USE OF THIS MEDICATION**Usual dose:**

Polymyxin B for Injection USP will be administered by a health care professional in a hospital or under direct supervision and monitoring by a healthcare professional. Although it is common to feel better early in the course of therapy, the medication should be used exactly as directed.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects are kidney problems such as albuminuria, cellular casts, diminishing urine output and rising BUN, neurological problems such as apnea, numbness, vertigo, blurred vision, facial flushing, and slurring of speech, pain at the injection site, skin redness and itching.

A hypersensitivity (allergic, anaphylactic) reaction with symptoms such as bronchoconstriction (narrowing of the breathing tubes) and interruption in breathing (apnea), rash, hives, itching, and swelling of tissues have been reported with inhaled polymyxin B sulphate.

This is not a complete list of side effects. For any unexpected effects while taking Polymyxin B for Injection USP, contact your doctor or pharmacist.

This leaflet was prepared by

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Last revised: November 9, 2011

HOW TO STORE IT

Before reconstitution: Store at room temperature 15- 30°C. Protect from light.

After reconstitution for Intravenous, Intramuscular, Intrathecal and Ophthalmic (Subconjunctival):

Reconstituted solutions should be stored under refrigeration (2-8°C) and the unused portion should be discarded after 24 hours.

After reconstitution for Ophthalmic (Topical): Reconstituted solutions should be stored under refrigeration (2-8°C). Any unused portion should be discarded after 72 hours.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, SteriMax Inc. at:
1-800-881-3550