Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution, USP* (Sterile)

Rx only

FOR TOPICAL APPLICATION IN THE EYE

*Does not meet USP packaging specification for light resistance.

DESCRIPTION
Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution, USP* is a sterile antimicrobial solution for topical ophthalmic use. It has a pH of 4.0 to 6.2 and an osmolality of 270 to 310 mOsm/kg.

Chemical Names:
Polymyxin B sulfate, 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine sulfate (2:1), is a white, odorless, crystalline powder with a molecular weight of 678.72 and the following structural formula:

\[
\text{C}_{37}\text{H}_{38}\text{N}_{10}\text{O}_{10}\text{S} \quad \text{Mol. Wt. 678.72}
\]

Polymyxin B sulfate is the sulfate salt of polymyxin B, a cyclic lipopeptide antibiotic, which is produced by the growth of Bacillus polymyxa (Prazmowski) Migula (Fam. Bacillaceae). It has a potency of not less than 6,000 polymyxin B units per mg, calculated on an anhydrous basis. The structural formula is:

\[
\text{CH}_{3}H_{2}\text{N}_{2}\text{O}_{5}\text{S}
\]

Polymyxin B is bactericidal for a variety of gram-negative organisms, especially Pseudomonas aeruginosa. It increases the permeability of the bacterial cell membrane by interacting with the phospholipid components of the membrane.

Blood samples were obtained from 11 human volunteers at 20 minutes, 1 hour and 3 hours following instillation in the eye of 2 drops of ophthalmic solution containing 1 mg trimethoprim and 10,000 units polymyxin B per mL. Peak serum concentrations were approximately 0.03 µg/mL trimethoprim and 0.011 µg/mL polymyxin B.

Microbiology: In vivo studies have demonstrated that the anti-infective components of trimethoprim sulfate and polymyxin B sulfate ophthalmic solution are active against the following bacterial pathogens that are capable of causing external infections of the eye: Tetracycline-resistant, including 64% (13/20) trimethoprim-resistant and 80% (16/20) polymyxin B-resistant isolates of S. aureus, 35% (7/20) trimethoprim-resistant and 25% (5/20) polymyxin B-resistant isolates of S. epidermidis, 88% (18/20) trimethoprim-resistant and 65% (13/20) polymyxin B-resistant isolates of E. coli, 100% (20/20) trimethoprim-resistant and 100% (20/20) polymyxin B-resistant isolates of K. pneumoniae, 42% (8/19) trimethoprim-resistant and 95% (18/19) polymyxin B-resistant isolates of P. aeruginosa, and 83% (14/17) trimethoprim-resistant and 100% (17/17) polymyxin B-resistant isolates of H. influenzae.

INDICATIONS AND USAGE
Polymyxin B sulfate and trimethoprim ophthalmic solution is indicated in the treatment of surface ocular bacterial infections, including acute bacterial conjunctivitis, and blepharoconjunctivitis, caused by susceptible strains of the following microorganisms: Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, and Pseudomonas aeruginosa.

CONTRAINDICATIONS
Polymyxin B sulfate and trimethoprim ophthalmic solution is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS
NOT FOR INJECTION INTO THE EYE: If a sensitivity reaction to polymyxin B solution occurs, discontinue use. Polymyxin B sulfate and trimethoprim ophthalmic solution is not indicated for the prophylaxis or treatment of opthalmia neonatorum.

PRECAUTIONS
As with other antimicrobial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Information for Patients:
Avoid contaminating the applicator tip with material from the eye, fingers, or other source. This precaution is necessary if the sterility of the drops is to be maintained.

If redness, irritation, swelling or pain persists or increases, discontinue use immediately and contact your physician. Patients should be advised not to wear contact lenses if they have signs and symptoms of ocular bacterial infections.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential have not been conducted with polymyxin B sulfate or trimethoprim.

Mutagenesis: Trimethoprim was demonstrated to be non-mutagenic in the Ames assay. In studies at two laboratories no chromosomal damage was detected in cultured Chinese hamster ovary cells at concentrations approximately 500 times human plasma levels after oral administration; at concentrations approximately 1,000 times human plasma levels after oral administration in these same cells, a low level of chromosomal damage was induced at one of the laboratories. Studies to evaluate mutagenic potential have not been conducted with polymyxin B sulfate.

Impairment of Fertility: Polymyxin B sulfate has been reported to impair the motility of equine sperm, but its effects on male or female fertility are unknown.
No adverse effects on fertility or general reproductive performance were observed in rats given trimethoprim in oral dosages as high as 70 mg/kg/day for males and 14 mg/kg/day for females.

Pregnancy:
- Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with polymyxin B sulfate. It is not known whether polymyxin B sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.
- Trimethoprim has been shown to be teratogenic in the rat when given in oral doses 40 times the human dose. In some rabbit studies, there were no abnormalities in the 10 children whose mothers received the drug during the first trimester. In a separate survey, Brumfitt and Pursell also found no congenital abnormalities in 35 children whose mothers had received oral trimethoprim and sulfamethoxazole at the time of conception or shortly thereafter.
- Because trimethoprim may interfere with folic acid metabolism, trimethoprim should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Nonteratogenic Effects: The oral administration of trimethoprim to rats at a dose of 70 mg/kg/day commencing with the last third of gestation and continuing through parturition and lactation caused no deleterious effects on gestation or pup growth and survival.
- Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when polymyxin B sulfate and trimethoprim ophthalmic solution is administered to a nursing woman.
- Pediatric Use: Safety and effectiveness in children below the age of 2 months have not been established (see WARNINGS).
- Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS
- The most frequent adverse reaction to polymyxin B sulfate and trimethoprim ophthalmic solution is local irritation consisting of increased redness, burning, stinging, and/or itching. This may occur on instillation, within 48 hours, or at any time with extended use. There are also multiple reports of hypersensitivity reactions consisting of lid edema, itching, increased redness, tearing, and/or circumocular rash. Photosensitivity has been reported in patients taking oral trimethoprim.

HOW SUPPLIED
- Polymyxin B Sulfate and Trimethoprim Ophthalmic Solution, USP*, containing 10,000 polymyxin B units and 1 mg trimethoprim per mL, is supplied in a plastic bottle with a controlled drop tip and a natural cap in the following size:
  - 10 mL - NDC 24208-315-10

DO NOT USE IF IMPRINTED NECKBAND IS NOT INTACT.

Storage: Store at 15°-25°C (59°-77°F). PROTECT FROM LIGHT.

*D does not meet USP packaging specification for light resistance.

RETAIN IN CARTON UNTIL TIME OF USE.

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Bridgewater, NJ 08807 USA
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