

PRODUCT MONOGRAPH

POLYTRIM

Trimethoprim Sulphate + Polymyxin B Sulfate

Ophthalmic Solution

Antibacterial Agent

Allergan Inc.
Markham, Ontario

2HN924360

DATE OF PREPARATION:

November 13, 1992

NAME OF DRUG

POLYTRIM*

(Trimethoprim Sulphate + Polymyxin B Sulfate)

THERAPEUTIC CLASSIFICATION

Antibacterial Agent

ACTIONS

POLYTRIM Ophthalmic Solution (trimethoprim Sulphate + polymyxin B sulfate) is a sterile antimicrobial solution for topical ophthalmic use. Trimethoprim is a synthetic antibacterial drug active against a wide variety of aerobic Gram-positive and Gram-negative ophthalmic pathogens. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. This binding is very much stronger for the bacterial enzyme than for the corresponding mammalian enzyme. For this reason, trimethoprim selectively interferes with bacterial biosynthesis of nucleic acids and proteins.

Polymyxin B, a cyclic lipopeptide antibiotic, is rapidly 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.

In combination, trimethoprim and polymyxin B are effective against a wide range of aerobic Gram-negative and Gram-positive bacterial pathogens capable of causing external infections of the eye.

INDICATIONS AND CLINICAL USE

POLYTRIM Ophthalmic Solution is active against the following Gram-positive and Gram-negative organisms which may be associated with surface ocular bacterial infections:

Gram-positive

Staphylococcus aureus
 Staphylococcus epidermidis
 Streptococcus spp.
 (Group A beta-hemolytic and
 non-hemolytic)
 Streptococcus pneumoniae

Gram-negative

Pseudomonas aeruginosa
 Haemophilus influenzae
 Haemophilus aegyptius
 Escherichia coli
 Klebsiella pneumoniae
 Proteus mirabilis
 (indole-positive)
 Proteus spp.
 (indole-negative)
 Enterobacter aerogenes
 Citrobacter freundii
 Citrobacter diversus
 Acinetobacter calcoaceticus
 Moraxella lacunata
 (some strains)
 Serratia marcescens

Sensitivity tests should be performed wherever possible to determine the optimum therapy for any given infection.

POLYTRIM Ophthalmic solution is indicated for the following surface ocular bacterial infections when caused by susceptible strains of the above organisms.

Acute bacterial conjunctivitis
 Blepharitis
 Blepharoconjunctivitis

CONTRAINDICATIONS

POLYTRIM 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 POLYTRIM occurs, discontinue use. POLYTRIM Ophthalmic Solution is not indicated for the prophylaxis or treatment of ophthalmia neonatorum.

PRECAUTIONS

General: As with other antimicrobial preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Information for Patients: Avoid contamination of the dropper with material from the eye, fingers, or other source. This precaution is necessary to maintain sterility of the drops.

If redness, irritation, swelling or pain persists or increases, discontinue use immediately and contact your physician.

Use in Children: The safety and effectiveness in children below the age of 2 months has not been established (see WARNINGS).

ADVERSE REACTIONS

The most frequent adverse reaction to POLYTRIM Ophthalmic Solution is local irritation consisting of transient burning or stinging, itching or increased redness upon instillation. These reactions occur in less than 4 of 100 patients treated. POLYTRIM has a low incidence of hypersensitivity reactions (less than 2 of 100 patients treated) consisting of lid edema, itching, increased redness, tearing and/or circumocular rash.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Poisoning is unlikely to occur from the ingestion of POLYTRIM. If poisoning does occur, remove the agent from the stomach by lavage and/or emesis. If renal function is normal, force fluids orally or parenterally to promote excretion.

In extreme overdosage in patients with impaired renal function, consideration should be given to dialysis as a means of both eliminating the drug from the blood and in reducing the risk of uremia. Calcium folinate (3 to 6 i.m. for 5 to 7 days) is an effective antidote for adverse effects in the hemopoietic system caused by trimethoprim.

DOSAGE AND ADMINISTRATION

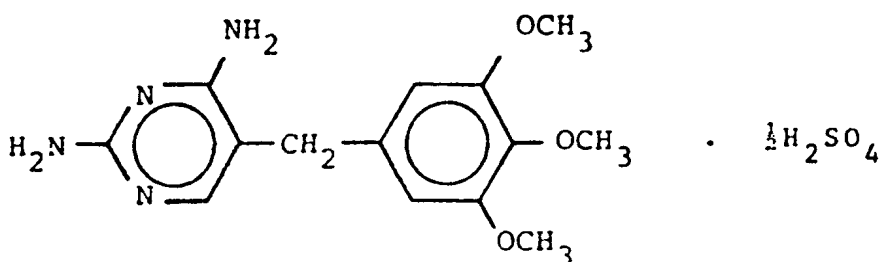
Adults: In mild to moderate infections, instill 1 or 2 drops in the affected eye every 3 hours (maximum of 6 doses per day) for a period of 7-10 days.

More severe infections may require instillation of 1 or 2 drops every hour until improvement is observed and then reduced to 1 or 2 drops every 3 hours.

Children: Children over two months of age are treated in the same manner as adults.

AVAILABILITY

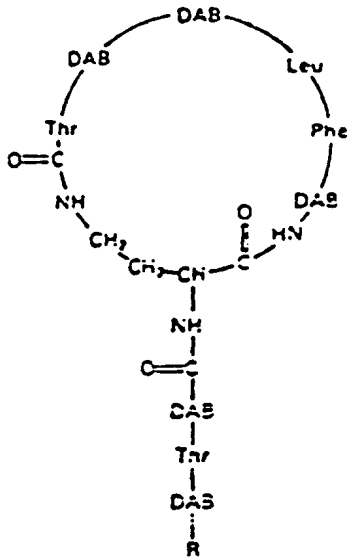
Bisporin Ophthalmic Solution is sterile and available in a 10 mL plastic Drop-dose dispenser. Each mL contains trimethoprim sulphate equivalent to 1 mg of trimethoprim and polymyxin B Sulphate 10,000 units. Store at 15-30°C and protect from light.

STRUCTURAL FORMULA AND CHEMISTRYTrimethoprim Sulfate

Molecular Formula: $C_{14}H_{18}N_4O_3 \cdot \frac{1}{2}H_2SO_4$ Molecular Weight: 339.36

Chemical Name: 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine sulfate (2:1).

Description: Trimethoprim sulfate is a white, odourless, crystalline compound with a melting range of 239°-242°C. The pH of a 0.05% (w/v) aqueous solution is between 4 and 5.

Polymyxin B

DAB = α,γ-diaminobutyric acid

Molecular Formula: $C_{56}H_{98}N_{16}O_{13}$
 $C_{55}H_{96}N_{16}O_{13}$

Molecular Weight: 1202/1188

Description:

Polymyxin B sulfate is a white to buff coloured powder which may have a faint sourlike odour. Polymyxin is a generic term for antibiotics derived from the fermentations of various media by the strain of *Bacillus polymyxa*. It is fully soluble in water (20 mg/mL) and slightly soluble in alcohol. The pH of an aqueous solution is between 5 and 7.5

MICROBIOLOGY

The in vitro spectrum of action of POLYTRIM encompasses most bacterial pathogens that cause external infections of the eye.

Trimethoprim is bacteriostatic against many Gram-negative and Gram-positive organisms with the most notable exception being *Pseudomonas aeruginosa*.² Polymyxin B is proven bactericidal against *Pseudomonas aeruginosa* as well as other Gram-negative bacteria.

Synergy has also been demonstrated in vitro for combinations of trimethoprim and polymyxin B against some bacteria.³⁻⁷

PHARMACOLOGY

When used topically, trimethoprim and polymyxin B are rarely sensitizing and absorption through intact skin and mucous membrane is insignificant.

Blood samples were obtained from eleven human volunteers at 20 minutes, 1 hour and 3 hours following instillation of two drops of a solution containing 1 mg trimethoprim and 10,000 units of polymyxin B per mL. On the nine previous days, each patient received two drops of solution four times per day.

No detectable levels of drug were noted with assay limits of 0.03 mg trimethoprim per mL of serum and 1 unit polymyxin B per mL of serum.

TOXICOLOGY

A study was undertaken to determine the effects of trimethoprim and polymyxin B (TP) on the eyes of normal human volunteers. In a double-blind comparative study, TP eye drops were administered to one eye and a saline control preparation to the other in each of 20 healthy volunteers. Dosage administered was one drop, four times daily for a period of ten days. The eyes were examined on days 3, 5, 8 and 11. Volunteers were questioned regarding possible side effects at the time of their visits.

TP drops caused significantly ($p < .05$) more stinging, gritty sensations and circumocular itching than the control drops. These three actions were always transient and almost invariably mild. A transient and minimal degree of redness was occasionally observed (8 occasions in 6 volunteers) in TP treated eyes. The mean scores of the redness were not significantly different to those of the control preparation.

A second study was done in normal human volunteers with TSP sterile ophthalmic solution. TSP contained trimethoprim (1 mg/mL), sulfacetamide (5 mg/mL) and polymyxin B (10,000 units/mL). The study was conducted in a double-blind, placebo-controlled fashion with each volunteer receiving TSP and vehicle into separate eyes. The dosage was two drops into each eye, four times a day for ten days. Ophthalmic evaluations were conducted before and after each instillation of the drops.

Forty-eight completed the study. Conjunctival erythema was observed after instillation of active drug with a frequency of 65%. Vehicle produced erythema after instillation in 32%.

Burning (stinging) was reported after 54% of the instillations with TSP. Burning was reported in 2.5% of eyes receiving vehicle. Cyclic changes in the amplitude of reactivity were noted depending on the day of the study. The overall severity of the reactions was mild.

No significant changes in urinalyses, hematograms and organ function tests were revealed during the study. Ophthalmic examinations including conjunctival, funduscopy and slitlamp photographs revealed nothing outstanding.

REFERENCES

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