UPDATE ON ACUTE BACTERIAL CONJUNCTIVITIS AND ANTIBIOTIC RESISTANCE IN PEDIATRIC- DERIVED ISOLATES

BIBIANA JIN REISER, MD, MS, AND ANDREW J. SCHUMAN, MD

ACUTE CONJUNCTIVITIS is a common problem in the pediatric age group, and most affected patients present to their primary care provider.1 According to available data up to 18% of young children are brought to a primary care provider at least once each year because of acute conjunctivitis.2 Acute conjunctivitis comprises a diverse group of diseases that can be broadly divided into infectious and non-infectious conditions. Bacterial or viral infection are the most common infectious causes of conjunctivitis in the pediatric population, with bacterial estimated to be responsible for 50% to 75% of cases.1-3 Allergy and trauma (mechanical or chemical) are the non-infectious causes of conjunctivitis.4

DIAGNOSING ACUTE BACTERIAL CONJUNCTIVITIS

The diagnosis of bacterial conjunctivitis is generally made clinically based on the findings from history and clinical examination and knowledge of the typical presenting symptoms of the most common causes of conjunctivitis (TABLE 1).1 However, these methods are sometimes insufficient for diagnosis, whereas laboratory testing may provide identification of specific pathogens.5 Bacterial conjunctivitis characteristically presents with a copious mucopurulent discharge that can lead to matting of the eyelids on waking. It usually begins in one eye but may quickly spread to the fellow eye. A history of upper respiratory infection or presence of lymphadenopathy is rare. Pain, tenderness, light sensitivity, and problems with vision are not typical with conjunctivitis. These findings warrant prompt referral to an ophthalmologist for further evaluation and management.

BACTERIAL CONJUNCTIVITIS ETIOLOGY

Streptococcus pneumoniae, Haemophilus influenzae, and less frequently Moraxella catarrhalis are the most common causes of bacterial conjunctivitis in the pediatric population.6 The etiology of these infections, however, may vary across the pediatric age spectrum. In older infants (＞1 year) and preschool age children, H. influenzae and S. pneumoniae are the most common causes, whereas S. aureus and coagulase-negative staphylococci are more often isolated in cases of bacterial conjunctivitis among school-age children, adolescents, and teens (TABLE 2).5,7-8 Infections caused by Pseudomonas aeruginosa are seen more often in older children, which may reflect an association with contact lens wear.8

TABLE 1. Differential diagnosis for common causes of pediatric conjunctivitis

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Allergic Conjunctivitis</th>
<th>Bacterial Conjunctivitis</th>
<th>Viral Conjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance of eye discharge</td>
<td>White stringy mucoid</td>
<td>Mucopurulent</td>
<td>Watery</td>
</tr>
<tr>
<td>Presence of erythema</td>
<td>Mild to moderate</td>
<td>Moderate to severe</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Moderate to severe</td>
<td>None to mild</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Bilateral eye involvement</td>
<td>Common</td>
<td>Unilateral initially</td>
<td>Rare</td>
</tr>
<tr>
<td>Presence of lymphadenopathy</td>
<td>None</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>None</td>
<td>Rare</td>
<td>Common</td>
</tr>
</tbody>
</table>

MANAGEMENT OF BACTERIAL CONJUNCTIVITIS

Bacterial conjunctivitis is usually a self-limiting infection that will resolve on its own in 1 to 2 weeks. Treatment with an ophthalmic antibiotic, however, will accelerate resolution of the infection and its symptoms.9 Other potential benefits...
of treatment with an ophthalmic antibiotic include allowing earlier return to school or daycare, limiting infection spread, preventing recurrence, and decreasing the risk for sight-threatening complications.8-11

Treatment selection for any bacterial infection is ideally based on knowledge of the causative organism via culturing and its profile of antibiotic resistance.4 Given the time to receive culture results, the diagnosis of bacterial conjunctivitis in clinical practice is usually made clinically and antibiotic treatment is empiric.8 A topical antibiotic with a broad spectrum of antimicrobial activity is recommended to cover the most common causes of bacterial conjunctivitis.8

There are many topical ophthalmic antibiotics with an FDA-approved indication for treatment of bacterial conjunctivitis in pediatric patients. Factors to consider in treatment selection include cost, patient allergies, required dosing frequency, which can affect compliance, and local bacterial resistance patterns.5,12 According to recent data from the nationwide Antibiotic Resistance Monitoring in Ocular MicRorganisms (ARMOR) Surveillance study on antibiotic susceptibility and resistance of pediatric-sourced ocular isolates, in vitro antibiotic resistance appears common among staphylococcal and pneumococcal isolates collected from pediatric patients with ocular infections.8 Awareness of recent data from the nationwide ARMOR surveillance study on antibiotic susceptibility and resistance of pediatric-sourced ocular isolates should be useful for clinicians when choosing empiric therapy for pediatric patients with bacterial conjunctivitis.8

**THE ARMOR STUDY**8,13

Initiated in 2009, ARMOR is the largest and only ongoing study monitoring resistance trends among ocular pathogens of concern. It tracks minimum inhibitory concentrations (MICs) for up to 16 antibiotics across 10 classes. The various antibiotic classes represent ophthalmic and nonophthalmic agents and include: fluoroquinolones (besifloxacin, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, and ofloxacin); macrolides (azithromycin); aminoglycosides (tobramycin); lincosamides (clindamycin); penicillins (oxacillin and penicillin); dihydrofolate reductase inhibitors (trimethoprim); polypeptides (polymyxin B); amphenicols (chloramphenicol); tetracyclines (tetracycline); and glycopeptides (vancomycin).

**TREATMENT SELECTION FOR ANY BACTERIAL INFECTION IS IDEALLY BASED ON KNOWLEDGE OF THE CAUSATIVE ORGANISM VIA CULTURING AND ITS PROFILE OF ANTIBIOTIC RESISTANCE.**

Participating sites in the United States, including ocular centers, community hospitals, and university hospitals, are invited to submit isolates of *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*. Staphylococci are classified as methicillin resistant (MR) or methicillin susceptible (MS) based on susceptibility to oxacillin. There are no limits on patient age for submitting samples in ARMOR, and a significant number of samples are obtained from the pediatric population.13

All microbiological testing for ARMOR is done at an independent central laboratory using broth microdilution techniques. The MIC results are interpreted as susceptible, intermediate, or resistant based on established systemic breakpoints. Systemic susceptibility breakpoints are not available for interpreting the MIC data for besifloxacin because it was developed to that found in systemic tissues after systemic administration. Thus, the MIC data can be used to interpret its potency against specific strains. The ARMOR data are subject to some limitations.9 Due to the infrequent practice of culturing bacterial pathogens in patients seen in community practice with bacterial conjunctivitis, there is potential sampling bias such that the isolates analyzed may be skewed toward more difficult cases and may not reflect resistance patterns in community-based practices. In addition, application of systemic breakpoints to define susceptibility to ocular treatments and thus the applicability to topically applied antibiotics may be of limited value. However, assuming that the drug concentration achieved in the conjunctiva after topical administration is at least equal to that found in systemic tissues after systemic administration, application of systemic breakpoints is an appropriate method to compare antibiotic susceptibilities among ocular bacterial pathogens.

The ARMOR analysis focusing on antibiotic resistance among pediatric-sourced ocular pathogens included 995 bacterial isolates obtained from pediatric patients across 67 clinical sites over an 8-year period from January 2009 through December 2016.8 The isolates included *H. influenzae* (n = 286), *S. aureus* (n = 284), CoNS (n = 213), *S. pneumoniae*
The study found that in vitro antibiotic resistance among the pediatric-sourced isolates was common among staphylococcal and pneumococcal isolates, and remain high over the 8-year period. Specifically, high rates of resistance to azithromycin were found among MS strains of S. aureus (MSSA, 42.8%; Figure 1A) and MSCoNS (Figure 2A, 57.1%). Methicillin-resistance was prevalent among staphylococci, and for both MRCoNS and MRSA isolates, the majority of antibiotics tested demonstrated resistance rates exceeding 20% (Figures 1B, 2B). S. pneumoniae isolates were generally susceptible to the tested antibiotics with the exception of azithromycin for which the resistance rate was 38%.

The data from the ARMOR study also showed that many methicillin-resistant staphylococci strains demonstrated multidrug resistance (MDR) resistance to ≥3 antibiotic classes. Specifically, MRSA isolates were 11 to 16 times more likely than MSSA isolates to be resistant to ciprofloxacin, azithromycin, or tobramycin, and MRCoNS isolates were 6 to 54 times more likely than MSCoNS strains to be resistant to ciprofloxacin, azithromycin, or tobramycin. Rates of MDR were 49% and 70% among MRSA and MRCoNS, respectively. The MIC data showed that among antibiotics that are commercially available for topical use, besifloxacin had the lowest MIC<sub>90</sub> value against gram-positive isolates, including MRSA, MRCoNS, and S. pneumoniae (Table 3). As noted by the study authors, these findings are consistent with those of previous studies that also reported besifloxacin had a lower MIC<sub>90</sub> compared with other fluoroquinolones for these species and suggests a potential for improved efficacy with besifloxacin, especially against MR staphylococcal infections on the ocular surface. The MIC<sub>90</sub> for besifloxacin against P. aeruginosa was comparable to that of other newer generation fluoroquinolones.

The findings from ARMOR offer a useful reference when clinicians are prescribing an antibiotic to treat bacterial infections.
**TREATMENT DECISIONS: APPLICATION OF THE ARMOR STUDY TO CLINICAL PRACTICE**

conjunctivitis. Encouragingly, the report shows that antibiotic resistance among ocular bacterial pathogens isolated from pediatric patients has generally not increased in recent years. Importantly, however, the data identify the presence of high levels of resistance among staphylococcal and pneumococcal isolates to some commonly used antibiotics. The data from the ARMOR study also showed that many methicillin-resistant staphylococci strains demonstrated concurrent resistance to other drug classes.

The data from ARMOR support considering besifloxacin 0.6% ophthalmic suspension (BESIVANCE®, Bausch + Lomb) as patients ≥1 year of age first-line therapy for bacterial conjunctivitis. Symptoms of bacterial conjunctivitis may resolve with effective ophthalmic antibiotic treatment.

Pediatricians who treat ocular infections may want to consider ARMOR study findings to help guide treatment decisions in suspected cases of bacterial conjunctivitis.

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**INDICATION**

BESIVANCE® (besifloxacin ophthalmic suspension) 0.6% is a quinolone antimicrobial indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: *Aerococcus viridans*, *CDC coryneform group G, Corynebacterium pseudodiphtheriticum*, *Corynebacterium striatum*, *Haemophilus influenzae, Moraxella catarrhalis, Moraxella lacunata, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus lugdunensis, Staphylococcus warneri*, *Streptococcus mitis group, Streptococcus oralis, Streptococcus pneumoniae, Streptococcus salivarius*.

*Efficacy for this organism was studied in fewer than 10 infections.

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**IMPORTANT SAFETY INFORMATION**

- BESIVANCE is not for injection into the eye.
- As with other anti-infectives, prolonged use of BESIVANCE may result in overgrowth of non-susceptible organisms, including fungi. If super-infection occurs, discontinue use and institute alternative therapy.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE.
- The most common adverse event reported in approximately 2% of patients treated with BESIVANCE was conjunctival redness. Other adverse events reported in patients receiving BESIVANCE occurring in approximately 1–2% of patients included: blurred vision, eye pain, eye irritation, eye pruritus and headache.
- Safety and effectiveness in infants below one year of age have not been established.

Please see full Prescribing Information for BESIVANCE on pages 5 & 6.

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**REFERENCES**

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BESIVANCE safely and effectively. See full prescribing information for BESIVANCE.
BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%, for topical ophthalmic use
Initial U.S. Approval: 2009

INDICATIONS AND USAGE
Initial U.S. Approval: 2009

DOSAGE AND ADMINISTRATION

The most common adverse reaction reported in 2% of patients treated with BESIVANCE was conjunctival redness.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch + Lomb, a division of Valeant Pharmaceuticals North America LLC, at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2018

1 INDICATIONS AND USAGE
BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%, is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:

*Efficacy for this organism was studied in fewer than 10 infections. (1)

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 USE IN SPECIFIC POPULATIONS
8 USE IN SPECIFIC POPULATIONS
9 USE IN SPECIFIC POPULATIONS
10 USE IN SPECIFIC POPULATIONS
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%, is indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria:


*Efficacy for this organism was studied in fewer than 10 infections. (1)

2 DOSAGE AND ADMINISTRATION
Invert closed bottle and shake once before use. Instill one drop in the affected eye(s) 3 times a day, 4 to 12 hours apart for 7 days. (2)

Ophthalmic suspension containing 6 mg/mL (0.6%) of besifloxacin.

3 DOSAGE FORMS AND STRENGTHS
Ophthalmic suspension: besifloxacin 6 mg/mL (0.6%) (3)

4 CONTRAINDICATIONS
None. (4)

5 WARNINGS AND PRECAUTIONS

5.1 Not for Injection into the Eye
5.2 Growth of Resistant Organisms with Prolonged Use
5.3 Avoidance of Contact Lenses: Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE. (5.3)

6 ADVERSE REACTIONS

6.1 Not for Injection into the Eye
6.2 Growth of Resistant Organisms with Prolonged Use
6.3 Avoidance of Contact Lenses: Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE. (6)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no available human data for the use of BESIVANCE during pregnancy to inform any drug-associated risks; however, systemic exposure to besifloxacin from ophthalmic administration is low [see Clinical Pharmacology (12.3)]. Oral administration of besifloxacin to pregnant rats during organogenesis or during the pre/postnatal period did not produce adverse embryofetal or offspring effects at clinically relevant systemic exposures [see Data].

Data
Animal Data
In an embryofetal development study in rats, the administration of besifloxacin at oral doses up to 1,000 mg/kg/day during organogenesis was not associated with visceral or skeletal malformations in rat fetuses, although this dose was associated with maternal toxicity (reduced body weight gain and food consumption) and maternal mortality. Increased post-implantation loss, decreased fetal body weights, and decreased fetal ossification were also observed. At this dose, the mean plasma concentrations measured in humans at the recommended human ophthalmic dose (RHOD). The No Observed Adverse Effect Level (NOAEL) for this embryofetal development study was 100 mg/kg/day (Cmax, approximately 20 mcg/mL; approximately 46,500 times the mean plasma concentrations measured in humans at the recommended human ophthalmic dose (RHOD).

In a prenatal and postnatal development study in rats, the NOAELs for both fetal/neonate and maternal toxicity were 100 mg/kg/day. At 1,000 mg/kg/day, pups weighed significantly less than controls and had a reduced neonatal survival rate. Attainment of developmental landmarks and sexual maturation was delayed, although surviving pups from this dose group that were reared to maturity did not demonstrate deficits in behavior, including activity, learning and memory, and their reproductive capacity appeared normal.

8.2 Lactation
Risk Summary
There are no data on the presence of BESIVANCE in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to besifloxacin following topical ophthalmic administration is low [see Clinical Pharmacology (12.3)], and it is not known whether measurable levels of besifloxacin would be present in maternal milk following topical ophthalmic administration.
The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for BESIVANCE, and any potential adverse effects on the breastfed infant from BESIVANCE.

8.4 Pediatric Use

The safety and effectiveness of BESIVANCE in infants below one year of age have not been established. The efficacy of BESIVANCE in treating bacterial conjunctivitis in pediatric patients one year or older has been demonstrated in controlled clinical trials [see Clinical Studies (14)].

There is no evidence that the ophthalmic administration of quinolones has any effect on bone weight bearing joints, even though systemic administration of some quinolones has been shown to cause arthropathy in immature animals.

8.5 Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%, is a sterile ophthalmic suspension of besifloxacin formulated with DuraSite®† (polycarbophil, edetate disodium dihydrate and sodium chloride). Each mL of BESIVANCE contains 6.63 mg besifloxacin hydrochloride equivalent to 6 mg besifloxacin base. It is an 8-chloro fluoroquinolone anti-infective for topical ophthalmic use.

Besifloxacin hydrochloride is a white to pale yellowish-white powder.

Each mL contains:

Active: besifloxacin 0.6% (6 mg/mL);

Inactives: polycarbophil, mannitol, polysorbate 407, sodium chloride, edetate disodium dihydrate, sodium hydroxide and water for injection.

Preservative: benzalkonium chloride 0.01%

BESIVANCE is an isotonic suspension with an osmolality of approximately 290 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Besifloxacin is a fluoroquinolone antibacterial [see Microbiology (12.4)].

12.2 Pharmacokinetics

Plasma concentrations of besifloxacin were measured in adult patients with suspected bacterial conjunctivitis who received BESIVANCE bilaterally three times a day (16 doses total). Following the first and last dose, the maximum plasma besifloxacin concentration in each patient was less than 1.3 ng/mL. The mean besifloxacin Cmax was 0.37 ng/mL on day 1 and 0.43 ng/mL on day 6. The average elimination half-life of besifloxacin in plasma following multiple dosing was estimated to be 7 hours.

12.4 Microbiology

Besifloxacin is an 8-chloro fluoroquinolone with an N-1 cyclopropyl group. The compound has activity against Gram-positive and Gram-negative bacteria due to the inhibition of both bacterial DNA gyrase and topoisomerase IV. DNA gyrase is an essential enzyme required for replication, transcription and repair of bacterial DNA. Topoisomerase IV is an essential enzyme required for partitioning of the chromosomal DNA during bacterial cell division. Besifloxacin is bactericidal with minimum bactericidal concentrations (MBCs) generally within one dilution of the minimum inhibitory concentrations (MICs).

The mechanism of action of fluoroquinolones, including besifloxacin, is different from that of aminoglycoside, macrolide, and β-lactam antibiotics. Therefore, besifloxacin may be active against pathogens that are resistant to these antibiotics and these antibiotics may be active against pathogens that are resistant to besifloxacin. In vitro studies demonstrated cross-resistance between besifloxacin and some fluoroquinolones.

In vitro resistance to besifloxacin develops via multiple-step mutations and occurs at a general frequency of < 3.3 x 10^-10 for Staphylococcus aureus and < 7 x 10^-10 for Streptococcus pneumoniae.

Besifloxacin has been shown to be active against most isolates of the following bacteria both in vitro and in conjunctival infections treated in clinical trials [see Indications and Usage (1)]:

- Aerococcus viridans
- CDC coryneform group G
- Corynebacterium pseudodiphtheriticum
- Corynebacterium striatum
- Haemophilus influenzae
- Moraxella catarrhalis
- Moraxella lacunata
- Pseudomonas aeruginosa
- Staphylococcus aureus
- Staphylococcus epidermidis
- Staphylococcus hominis
- Staphylococcus lugdunensis
- Staphylococcus warneri
- Streptococcus mitis group
- Streptococcus oralis
- Streptococcus pneumoniae
- Streptococcus salivarius

*Efficacy for this organism was studied in fewer than 10 infections.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to determine the carcinogenic potential of besifloxacin have not been performed.

No in vitro mutagenic activity of besifloxacin was observed in an Ames test (up to 3.33 mcg/plate) on bacterial tester strains Salmonella typhimurium TA98, TA100, TA1535, TA1537 and Escherichia coli WP2uvrA. However, it was mutagenic in S. typhimurium strain TA102 and E. coli strain WP2 (pKM101). Positive responses in these strains have been observed with other quinolones and are likely related to topoisomerase inhibition.

Besifloxacin induced chromosomal aberrations in CHO cells in vitro and it was positive in an in vivo mouse micronucleus assay at oral doses ≥ 1,500 mg/kg. Besifloxacin did not induce unscheduled DNA synthesis in hepatocytes cultured from rats given the test compound up to 2,000 mg/kg by the oral route.

In a fertility and early embryonic development study in rats, besifloxacin did not impair the fertility of male or female rats at oral doses of up to 500 mg/kg/day. This dose is approximately 2,500 times higher than the mean plasma concentration measured in humans at the recommended ophthalmic dose.

14 CLINICAL STUDIES

In a randomized, double-masked, vehicle-controlled, multicenter clinical trial, in which patients 1-98 years of age were dosed 3 times a day for 5 days, BESIVANCE was superior to its vehicle in patients with bacterial conjunctivitis. Clinical resolution was achieved in 49% (90/191) for the BESIVANCE-treated group versus 33% (63/191) for the vehicle-treated group (difference 12%, 95% CI 3% - 22%). Microbiological outcomes demonstrated a statistically significant eradication rate for causative pathogens of 91% (181/198) for the BESIVANCE-treated group versus 60% (114/191) for the vehicle-treated group (difference 31%, 95% CI 23% - 40%). Microbiological eradication does not always correlate with clinical outcome in anti-infective trials.

16 HOW SUPPLIED/STORAGE AND HANDLING

BESIVANCE® (besifloxacin ophthalmic suspension) 0.6%, is supplied as a sterile ophthalmic suspension in a white low density polyethylene (LDPE) bottle with a controlled dropper tip and ten polypropylene cap. Tamper evidence is provided with a shrink band around the cap and neck area of the package.

NDC 24208-446-05 5 mL in 7.5 mL bottle

Storage:

17 PATIENT COUNSELING INFORMATION

Handing the Container

Advise patients to avoid contaminating the applicator tip with material from the eye, fingers or other source.

Use with Contact Lenses

Advise patients not to wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of therapy with BESIVANCE.

Dosing Instructions

Patients should be instructed to invert closed bottle (upside down) and shake once before each use.

Distributed by:

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Bridgewater, NJ 08807 USA

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