The Battle of the Bugs: 
Treating Infections in the Age of Resistance

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The Age of Modern Medicine

- Alexander Fleming is considered to be the father of modern medicine
  - He discovered penicillin more than 70 years ago (1928)
    - Considered to be one of the most significant medical breakthroughs of the twentieth century
  - Ernest Duchesne was the 1st to describe the antibiotic properties of Penicillium sp.
    - 1897

Prior to Penicillin, the # 1 war-time killer was infection
- Began being mass produced in 1943
  - Physicians were finally able to treat many diseases and childhood infections
  - This marked a new era in modern medicine
- Within 4 yrs of its release, resistance to penicillin began popping up and grew at an alarming rate

How Resistance Develops

- Bacterial become resistant when a mutation occurs in the DNA that protects the bacteria from a chemical
  - Mutation is only significant if the bacteria colony is exposed to the drug
- “Survival of the fittest” dictates survival occurs in only those capable of mutating

The Age of Modern Medicine

- By the mid-1940s and early 1950s streptomycin, chloramphenicol, and tetracycline had been discovered and the age of antibiotic therapy was underway
- These new antibiotics were very effective against a number of different pathogens including Gram (+) and gram (-) bacteria, intracellular parasites, and tuberculosis.
- The mass production of antimicrobials provided a temporary advantage in the struggle with microorganisms
  - Despite these rapid advances resistance quickly followed
Resistant Bacteria

- For any given bacterial population, random mutations will arise.
- With strong external selection pressures, these mutations will be favored resulting in resistant bacteria.
- American Academy of Microbiology:
  - 17.8 million pounds of antibiotics are used in animals each year.
  - Human exposure of these antibiotics is significant.

Bacterial Resistance

The problem is....

Antibiotics are used extensively:
- Topically
- Systemically
- Agriculturally as a growth stimulant
  - Most significant use of fluoroquinolones

Factors Implicated in Growing Rates of Antibiotic Resistance

- Microbiological:
  - Antibiotic misuse
- Environmental Factors:
  - Aging population
  - Social behavior
  - AIDS
  - International travel
- Technical Factors:
  - Increasing surgical intervention
  - Organ replacement
  - Life support systems

Susceptibility of Multidrug-Resistant Bacteria

- 256 bacterial strains isolated from 164 patients undergoing intraocular surgery b/w 1/2002 10/2002
- 124 (76%) coagulase-negative Staphylococci
- High level of resistance to penicillin, aminoglycosides, macrolides, ciprofloxacin, ofloxacin
- Gatifloxacin and moxifloxacin had the lowest resistance frequency in the fluoroquinolones antibiotic group
- Newer-generation fluoroquinolones provide excellent broad-spectrum coverage against bacterial flora isolated from conj, despite the high % of multidrug-resistant bacteria

Widespread Resistance to Older Antibiotics

- Methicillin-Resistant Staphylococcus Aureus (MRSA)
Staphylococcus Aureus

- Common bacteria usually found on the skin or in the nose
- Can cause a range of illnesses from minor skin infections such as pimples, impetigo, boils, cellulitis and abscesses...
- To life-threatening diseases such as pneumonia, meningitis, endocarditis, and septicemia
- There are many different types of staphylococcus aureus

Staphylococcus Aures Pharmacology

- MRSA is a particular strain of staphylococcus aureus that does not respond (is resistant) to many antibiotics
- *S aureus* was sensitive to penicillin when the drug was 1st introduced, but resistance developed almost immediately as the organism acquired a β-lactamase enzyme that was capable of inactivating drug

Staphylococcus Aures Pharmacology

- Methicillin was an antibiotic used many years ago to treat patients with *Staphylococcus aureus* infections
- It is now no longer used except as a means of identifying this particular type of antibiotic resistance

MRSA

- 1st outbreak identified in 1960 's
- Predominantly seen in hospitals, chronic care facilities and parenteral drug abusers
- The prevalence of MRSA isolates in hospitals in the US has risen steadily, such that now about ¼ nosocomial isolates are methicillin resistant

MRSA

- Community-acquired MRSA is becoming a significant problem, with the prevalence of MRSA among community isolates expected to reach as high as 25% in the next decade

Reasons for Rise of MRSA

- More powerful strains of MRSA developing
- An increased number of very sick people in hospital
- More complex medical treatments
  - The use of central lines and catheters
  - Patients move within and between hospitals more often
- High workloads which result in less compliance with routine hand washing
Multi-Drug Resistant Bacteria
- Emerging resistance of *S. aureus* has also been demonstrated for streptomycin, tetracycline, chloramphenicol, erythromycin and third-generation fluoroquinolones.
- The topical 4th Generation fluoroquinolones are more potent against MRSA than prior generation fluoroquinolones.
  - They inhibit both DNA gyrase and topoisomerase IV, requiring two genetic mutations for the bacteria to become resistant.

MRSA
- About 1/3 of people carry MRSA on their skin or in their nose without knowing it.
- These people are said to be ‘carriers’ of MRSA.
  - The bacteria are present on the body but don’t cause any harm.
  - This is also referred to as being ‘colonised’ with MRSA.
- Most people who carry MRSA in this way don’t go on to develop an infection.

Risk Factors for MRSA
- Prolonged hospital stays
- Prior surgery
- Seriously ill in intensive care
- Immunocompromised

2005: Deaths from MRSA Surpassed AIDS
- In 2005, AIDS killed 17,011 Americans.
- CDC reports > 90,000 get the potentially deadly "superbug" infections annually.
- Recent JAMA surveillance study, only about ¼ of MRSA infections involved hospitalized patients.
  - More than half were in the health care system.
    - People who had recently had surgery or were on kidney dialysis.
    - Open wounds and exposure to medical equipment are major ways the bug spreads.

MRSA Facts
- MRSA has evolved into a multitude of genetically distinct strains that vary widely in drug resistance, transmissibility and virulence.

MRSA Facts
- Non-healthcare workers are now just as likely as healthcare workers to carry MRSA on the conjunctiva and lid margin.
**MRSA Fact**

- While CA-MRSA strains tend to be less multi-drug resistant, some strains are associated with unusually invasive infections of the eye and orbit
  - USA300 clone – CA-MRSA with the PVL virulence marker

**Ocular Involvement of MRSA**

**4th Gen FQ Resistant Bacterial Keratitis after Refractive Surgery**


- 2 Cases of Bacterial Keratitis resistant to 4th Gen FQ
  - 1st pt – Pseudomonas following PRK -> had been treated with Vigamox
  - 2nd pt – MRSA following LASIK treated with Zymar …and Vigamox
  - Culture susceptibilities resistance to both 4th Gen FQ

**13 Cases of MRSA Following Refractive Surgery**

- Multicenter, retrospective chart review of 13 cases of MRSA keratitis following refractive surgery
  - 9 were either healthcare workers or exposed to a hospital surgical setting
  - 7 pts were prescribed 3rd generation FQ, 1 pt prescribed tobramycin, 1 pt was prescribed erythromycin and 3 were prescribed a 4th generation FQ

**Methicillin-Resistant Staphylococcus aureus Infectious Keratitis Following Refractive Surgery**

- A retrospective chart review of cases occurring between May 2002 and February 2005 in 10 referral cornea and refractive disease practices

**Prophylactic Antibiotics**

- Tobramycin 1/13 patients (7.7%)
- Erythromycin 1/13 patients (7.7%)
- Third-generation Fluoroquinolones 7/13 patients (53.4%)
- Unknown, 1 (bilateral)/13 patients (7.7%)
-Fourth-generation Fluoroquinolones 3/13 patients (23.1%)

**BPEI Ocular MRSA Trends-2000-2005**

### 2009 MRSA vs. MSSA

<table>
<thead>
<tr>
<th></th>
<th>Conjunctiva</th>
<th>Cornea</th>
<th>Cl. Cep</th>
<th>Staphylococci aureus</th>
<th>Coagulase-negative staphylococci (CNS)</th>
<th>Streptococcus pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>26</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>104</td>
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<tr>
<td>MRSA</td>
<td>19</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>69</td>
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<tr>
<td>TOTAL</td>
<td>45</td>
<td>44</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>173</td>
</tr>
<tr>
<td>%MRSA</td>
<td>42%</td>
<td>50%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>40%</td>
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</table>

### Results Ocular TRUST 3

<table>
<thead>
<tr>
<th>Isolates Submitted in Ocular TRUST (OT) 1-3</th>
<th>OT 1</th>
<th>OT 2</th>
<th>OT 3</th>
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<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>197</td>
<td>155</td>
<td>162</td>
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<tr>
<td>Methicillin-susceptible (MSSA)</td>
<td>164</td>
<td>71</td>
<td>84</td>
</tr>
<tr>
<td>Methicillin-resistant (MRSA)</td>
<td>33</td>
<td>84</td>
<td>78</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci (CNS)</td>
<td>—</td>
<td>92</td>
<td>79</td>
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<tr>
<td>Methicillin-susceptible (MSSA)</td>
<td>40</td>
<td>30</td>
<td>49</td>
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<tr>
<td>Methicillin-resistant (MRSA)</td>
<td>52</td>
<td>56</td>
<td>49</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>49</td>
<td>198</td>
<td>121</td>
</tr>
</tbody>
</table>

### Methicillin-Susceptible CNS

![Graph showing % isolates susceptible for various antibiotics for MSSA and MRSA]

### Methicillin-Resistant S. aureus

![Graph showing % isolates susceptible for various antibiotics for MSSA and MRSA]

### 2009 MRSA

<table>
<thead>
<tr>
<th>Drug Susceptibilities</th>
<th>Conjunctiva samples</th>
<th>Cornea samples</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MSSA</td>
<td>MRSA</td>
<td>MSSA</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>28</td>
<td>22</td>
<td>48</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>92</td>
<td>82</td>
<td>131</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>96</td>
<td>68</td>
<td>164</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>86</td>
<td>86</td>
<td>172</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>96</td>
<td>96</td>
<td>192</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>100</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

### In vitro Susceptibility for Select/Common Ocular Drugs.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MSSA (%)</th>
<th>MRSA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=190</td>
<td>N=84</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>98</td>
<td>43</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>100</td>
<td>85</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>93</td>
<td>25</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>91</td>
<td>31</td>
</tr>
<tr>
<td>Trimethoprim-sulfa</td>
<td>99</td>
<td>92</td>
</tr>
</tbody>
</table>
**Infectious Keratitis in Refractive Eye Care**

- Clinicians must be alert to the postop patient with signs and symptoms of possible post-LASIK and post-PRK infectious keratitis.
- PRK: Corneal scrapings, cultures, and sensitivities of all cases of focal infiltrates
- LASIK: Lifting the flap, scraping, culturing, and obtaining sensitivities on all cases of focal infiltrates

**Precautions for Healthcare Workers**

- Patients exposed to healthcare facilities who are at higher risk of infection from nosocomial MRSA, prophylactically treat blepharitis with lid hygiene and hot compresses preoperatively
- Consider a nasal swab for MRSA carriage
- Consider bacitracin or a fourth-generation fluoroquinolone or bacitracin for preoperative prophylaxis

**Treatment of MRSA s/p LASIK**

- Irrigating under the flap with fortified vancomycin (50 mg/ml)
- Antibiotics to include better coverage for MRSA-fortified vancomycin every 30 minutes, alternating with topical 4th Gen q 30 min
- Bacitracin ointment or Neosporin ointment to the eyelids qid

**Tracking Resistance**

**TRUST**

- Tracking Resistance in U.S. Today (TRUST)
- In vitro susceptibility testing is performed by an independent central laboratory on isolates submitted annually by 200 or more clinical laboratories across all 50 states
- Ocular isolates periodically have been submitted for testing in the TRUST program, but no national surveillance program systematically has tracked in vitro susceptibility in ocular isolates
Ocular TRUST

- Expansion of the TRUST program to include an ocular-specific substudy that annually will monitor in vitro susceptibility of pathogens isolated from ocular infections

Ocular TRUST

- Annually evaluates in vitro antimicrobial susceptibility of:
  - *Staphylococcus aureus*
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
- To ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, penicillin, azithromycin, tobramycin, trimethoprim, and polymyxin B in national samples of ocular isolates

Ocular TRUST Tracking Resistance in the United States Today

- Ocular TRUST is the only nationwide surveillance program to monitor antimicrobial susceptibility in prospectively collected ocular isolates

151 *S. aureus* isolates
51 *S. epidermidis* isolates
188 *S. pneumoniae* isolates

Asbell PA et al. Ocular TRUST AJO March 2008

Ocular TRUST

- Staphylococci susceptibilities to levofloxacin, gatifloxacin and moxifloxacin were identical, regardless of species or methicillin status
- *S. aureus* had a 52% susceptibility rate
  - MRSA had an 18% susceptibility rate
  - Methicillin-sensitive *S. aureus* (MSSA) had a 93% rate
- *S. epidermidis* had a 55% rate
  - MRSE = 32% susceptibility rate
  - MSSE = 90% susceptibility rate

Macrolides (Azithromycin)

- MRSA had an 8% susceptibility rate, MSSA had a 62% rate
- MRSE had a 13% rate and MSSE had 40% rate

Asbell PA et al. Ocular TRUST AJO March 2008
Ocular TRUST

- All *S. pneumoniae* isolates were susceptible to levofloxacin, gatifloxacin and moxifloxacin
- 69% were susceptible to treatment with azithromycin.

Our Arsenal of Antimicrobial Therapy

The Arsenal

- **Fluoroquinolones**
  - Ciprofloxacin
  - Levofloxacin
  - Gatifloxacin
  - Moxifloxacin
- **Aminoglycosides**
  - Tobramycin
  - Gentamycin
- **Macrolides**
  - Erythromycin
  - Bacitracin
  - Azithromycin
- **Dihydrofolate reductase inhibitors**
  - Trimethoprim
- **Polypeptides**
  - Polymixin B

Fluoroquinolones

- 1st released for ophthalmic use in early 1990’s
- Represented an important breakthrough for clinicians
- For the 1st time strong commercially available antibiotics available to treat bacterial conjunctivitis and ulcerative keratitis
- Broad spectrum including pseudomonas

Ophthalmic Antibiotics: Fluoroquinolones

- The first safe broad-spectrum ophthalmic agents
- Revolutionized treatment of severe corneal infections
- Very low sensitization rate
- Excellent safety profile
- Comfortable
- No reports of systemic effects

Fluoroquinolones

- The BIG problem with the fluoroquinolones has been bacterial resistance!
  - 1993 – 5.8% resistance
  - 2 yrs after release of fluoroquinolones
  - 1997 – 35% bacterial resistance
  - 2001 – 100% resistance to staph aureus isolates cultured in endophthalmitis
    - Resistance to cipro, oflox, levofox

*Ophthalmology* July 1999; 106 (7): 1313-8
**Resistance to FQ's**


9 yr period: 2920 cultures; 1468 (50%) recovered

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>1998</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bact Keratitis</strong></td>
<td>196</td>
<td>137</td>
</tr>
<tr>
<td><strong>Resistance to Staph Aures</strong></td>
<td>11% Cipro and Oflox</td>
<td>28% Cipro and Oflox</td>
</tr>
<tr>
<td><strong>Resistance to Pseudomonas</strong></td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Staph aures</strong></td>
<td>(27) 29%</td>
<td>(32) 48%</td>
</tr>
<tr>
<td><strong>Pseudomonas</strong></td>
<td>(51) 54%</td>
<td>(32) 46%</td>
</tr>
</tbody>
</table>

**Resistance to FQ’s**

Goldstein et al. Ophthalmology July 1999; 106 (7): 1313-8

1053 Isolates from 825 Cases 1993 to 1997

<table>
<thead>
<tr>
<th></th>
<th>1993</th>
<th>1997</th>
</tr>
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<tbody>
<tr>
<td><strong>Bact Keratitis</strong></td>
<td>284</td>
<td>75</td>
</tr>
<tr>
<td><strong>Resistance to Staph Aures</strong></td>
<td>5.8% Cipro</td>
<td>4.7% Oflox</td>
</tr>
<tr>
<td><strong>Resistance to Pseudomonas</strong></td>
<td>51%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Gram +</strong></td>
<td>81.8%</td>
<td>51.4%</td>
</tr>
<tr>
<td><strong>Gram -</strong></td>
<td>18.2%</td>
<td>48.6%</td>
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**Widespread Decline in Susceptibility to 3rd-Generation Fluoroquinolones**

In Vitro Susceptibility of Staphylococcus aureus to 3rd-Generation Fluoroquinolones: Campbell Laboratory Survey


**Fluoroquinolones: Resistance**

- In vitro tests that compare moxifloxacin with other fluoroquinolones suggest that moxifloxacin is less likely to
  - Be affected by genetic mutations
  - Select for resistance


**4th Generation Fluoroquinolones**

- Developed to address the issues of resistance
- Developed to allow for broader coverage for both gram (+) and gram (-) organisms
  - Better gram (+) coverage is needed as the growing trend towards more gram (+) infections

**Mechanism of Action: Fluoroquinolones**

- Cause lethal breaks in the bacterial chromosome at their target site
- Targets of 3rd-generation FQs
  - DNA gyrase in Gram-negatives
  - Topo IV in Gram-positives
- Targets of 4th-generation FQs are dual binding
  - DNA gyrase AND topo IV in both Gram-positives and Gram-negatives
Gatifloxacin and Moxifloxacin
Comparison of In Vitro Efficacy

Fourth-Generation Fluoroquinolones More Effective Than Older-Generation Fluoroquinolones
Staphylococcal Endophthalmitis Isolates More Susceptible to Fourth Generation Fluoroquinolones than to Older Fluoroquinolones

Gatifloxacin vs Moxifloxacin, MIC\textsubscript{90} for Gram-positive Isolates

Gatifloxacin vs Moxifloxacin, MIC\textsubscript{90} for Gram-negative Isolates
Mean MICs for the active ingredients in the fourth-generation fluoroquinolone using clinical isolates (N = 34)

Gram-positive Pathogen

<table>
<thead>
<tr>
<th></th>
<th>n = 6</th>
<th>n = 6</th>
<th>n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.00035</td>
<td></td>
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Comparing Molecules: Gatifloxacin vs Moxifloxacin In Vitro

Comparing Commercial Formulations: ZYMAR® vs Vigamox® In Vitro

Staphylococcus aureus
Streptococcus pneumoniae
Staphylococcus epidermidis

Methicillin-resistant S. epidermidis

Mean MIC (μg/mL)

In vitro data. Clinical significance not known.

Comparing Molecules:
Gatifloxacin vs Moxifloxacin

Comparing Commercial Formulations:
ZYMAR® vs Vigamox®

In Vitro

Rate of Endophthalmitis: Third- vs Fourth-Generation Fluoroquinolones

- A retrospective, cross-sectional (prevalence) study of patients who had phacoemulsification at a university eye center over a 10-year period.
- The main outcome measure was the occurrence of endophthalmitis after cataract surgery.
  - Third-generation fluoroquinolones (ciprofloxacin, ofloxacin) were used as prophylactic antibiotics from January 1997 to August 2003.
  - Fourth-generation fluoroquinolones (gatifloxacin, moxifloxacin) were used as prophylactic antibiotics from September 2003 to December 2007.
- A nosocomial infectious reporting database was used to report endophthalmitis occurrences.
- Prospectively collected data were retrospectively analyzed to establish endophthalmitis rates.

Ten-Year Retrospective Comparison of Endophthalmitis after Cataract Surgery

Four-Year Retrospective Comparison of Endophthalmitis after Cataract Surgery

- During the period of 1997 to 2003.
- During the period of 2003 to 2007.

Besivance: FDA Approval May 29, 2009

Besifloxacin

- Novel fluoroquinolone (Chemical Structure)
- Broad spectrum bactericidal activity
- Balanced dual targeting of DNA topoisomerases
- Low incidence of resistance development
- Superior activity vs. multidrug-R staph
Besivance

- TID for 5 days
- FDA approved for 7 days
- 0.6% suspension

Proksch J, Driot JY, Ward KW. Nonclinical Ocular and Systemic Pharmacokinetics of BOL-303224-A, a Novel Fluoroquinolone Antimicrobial Agent for Topical Ophthalmic Use. ARVO 2007

Dosing

In patients 1 year of age or older:

- Instill 1 drop every 2 hours in the affected eye(s) while awake, up to 8 times on day 1
- Instill 1 drop 2 to 4 times daily in the affected eye(s) while awake on days 2 through 7

ZYMAXID™ (gatifloxacin ophthalmic solution) 0.5% performed well in clinical trials when dosed BID.

Dosing ZYMAXID™ 4 times a day delivers more drug to the eye, taking full advantage of the higher concentration of gatifloxacin.

Ophthalmic Solutions of Fourth-Generation Fluoroquinolones

<table>
<thead>
<tr>
<th>Approval year</th>
<th>ZYMAR®</th>
<th>Vigamox®</th>
<th>Besivance™</th>
<th>ZYMAXID™</th>
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<tbody>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2003</td>
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</tr>
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<td>2009</td>
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<tr>
<td>2010</td>
<td></td>
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</table>

- Indications: Bacterial conjunctivitis
- Active Ingredient: Gatifloxacin 0.3%, Moxifloxacin 0.5%, Besifloxacin 0.6%, Gatifloxacin 0.5%
- Preservative: 0.005% BAK, No preservative, 0.01% BAK, 0.005% BAK
- Package size/mean drops: 5 mL/132 mean drops per bottle, 3 mL/82 mean drops per bottle, 5 mL, 2.5 mL/83 mean drops per bottle

*BAK = benzalkonium chloride.

*Dosette™ mean drops not yet calculated.