Class Update with New Drug Evaluation: Ototopical Antibiotics

Month/Year of Review: May 2015

New Drug: Finafloxacin

Current Status of PDL Class:
See Appendix 1.

Research Questions:
- Is there evidence of superior clinical efficacy/effectiveness of one ototopical antibiotic or antibiotic/corticosteroid combination over another for clinical resolution of acute otitis externa or for acute otitis media specifically in patients with tympanostomy tubes?
- Is there evidence of decreased harms of one ototopical antibiotic or antibiotic/corticosteroid combination over another when used to treat acute otitis externa or for acute otitis media specifically in patients with tympanostomy tubes?
- Are there subgroups of patients based on demographics, concomitant medications, or co-morbidities for which one ototopical antibiotic or antibiotic/corticosteroid combination is more effective or associated with less harms when used for these conditions?

Conclusions and Recommendations:
- There is insufficient evidence that one ototopical antibiotic or antibiotic/corticosteroid combination has superior clinical efficacy or comparative effectiveness over another product for clinical resolution of acute otitis externa.
- There is insufficient evidence that either ofloxacin or ciprofloxacin/dexamethasone, the only ototopical drugs with FDA indications for treating otitis media specifically in patients with tympanostomy tubes, is more efficacious or safer than the other for this indication. Since these patients have received multiple systemic antibiotics for acute otitis media prior to getting tympanostomy tube placement, higher rates of antibiotic resistance may be noted in these patients and the use of a broad spectrum quinolone antibiotic is appropriate. There is insufficient evidence for all other ototopical antibiotics or antibiotic/corticosteroid combinations for this indication.
- There is low quality evidence that ototopical quinolone antibiotics or quinolone/corticosteroid combinations may be safer than ototopical aminoglycoside antibiotics in patients with tympanostomy tubes due to potential risk for adverse effects from systemic absorption of the aminoglycoside in the inner ear.
- Keep either ofloxacin or ciprofloxacin/dexamethasone as a preferred product for treatment of acute otitis media in patients with tympanostomy tubes.
- Keep at least one ototopical aminoglycoside antibiotic as an option for otitis externa.
- Maintain finafloxacin as non-preferred due to its limited indication for otitis externa only and lack of comparative evidence, unless it is cost-effective.
- Review comparative drug costs in the executive session.

Author: A. Gibler, Pharm.D.  Date: May 2015
**Purpose for Class Update:**
The otic antibiotic drug class has not been formally reviewed by the Pharmacy and Therapeutics Committee since 2010. In addition, finafloxacin was recently approved as a new otic antibiotic by the U.S. Food and Drug Administration (FDA) in December 2014.

**Previous Conclusions:**
- No evidence was found to support a difference in efficacy/effectiveness between drug products of this class.
- No evidence was found to support a difference in harms between drug products of this class.

**Background:**
Acute otitis externa (AOE), also known as “swimmer’s ear”, is one of the most common infections encountered by clinicians. In 2007, there were 2.4 million visits to ambulatory care centers and emergency departments for AOE, with 600,000 hours spent by clinicians treating AOE and one-half billions dollars in direct costs. Half of all cases occur in children 5 to 14 years of age. AOE is characterized by rapid onset and diffuse inflammation of the external ear canal, which may also involve in pinna or tympanic membrane. Symptoms of AOE commonly include severe otalgia, itching or fullness and hearing loss may occur. AOE is a cellulitis of the ear canal skin and subdermis that occurs with acute inflammation and edema. Nearly all cases of AOE in North America are polymicrobial, the most common pathogens involving *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Ototopical antibiotics are beneficial for AOE but oral antibiotics have limited utility. Nonetheless, 20-40% of patients with AOE receive oral antibiotics, which are usually inactive against *P. aeruginosa* and *S. aureus*, have undesirable side effects, and serve to select out resistant organisms. Bacterial resistance is less concern with ototopical antibiotics because the high local concentration of drug in the ear canal will eradicate all susceptible organisms plus those that may otherwise be resistant to systemically administered antibiotics (which only achieve concentrations at the site of infection several magnitudes lower than when topically administered).

Acute otitis media (AOM) typically an acute onset of symptoms with presence of otalgia, middle ear effusion and signs of acute middle ear inflammation. AOM remains the most common condition for which antibiotics are prescribed for children in the U.S. Insertion of tympanostomy tubes is primarily performed in children with recurrent AOM and persistent middle ear effusion in order to reduce the incidence of future infections and, should AOM occur with tubes in place, the ability to manage infections with ototopical antibiotics. Tympanostomy tubes can serve as a drug-delivery device, allowing concentrated antibiotic eardrops to reach to middle ear space directly through the tube lumen and reducing the use of systemic antibiotics. Otorrhea is common after placement of tympanostomy tubes, with a mean incidence of 26% (range, 4%-68%) in observational studies. Most otorrhea is sporadic, brief, and relatively painless, with recurrent otorrhea affecting only about 7% of patients and chronic otorrhea occurring in about 4%. Acute delayed otorrhea is usually a manifestation of AOM and is caused by the typical nasopharyngeal pathogens *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*. Conversely, when acute otorrhea occurs after water exposure (e.g., bathing or swimming) or in older children, it is often caused by external auditory canal pathogens such as *P. aeruginosa* and *S. aureus*.

All ototopical antibiotic and antibiotic/corticosteroid combination have an indication for otitis externa. However, ofloxacin and ciprofloxacin/dexamethasone have additional indications for otitis media in children with tympanostomy tubes. In general, broad-spectrum quinolone drugs will cover *P. aeruginosa, S. aureus, S. pneumoniae, H. influenza* and *M. catarrhalis*. The relevant outcome for these antibiotics in clinical studies is resolution of AOE and AOM in patients with tympanostomy tubes, which implies clinical resolution of all signs and symptoms (e.g., pain, fever, otorrhea).

Author: A. Gibler, Pharm.D. Date: May 2015
Methods:
A Medline literature search from 2010 to present for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls was conducted. The Medline search strategy used for this review is available in Appendix 3, which includes dates, search terms and limits used. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Due to the differences in international bacterial susceptibility, only studies performed in the United States were considered.

Systematic Reviews:
None identified.

New Guidelines:
The American Academy of Otolaryngology—Head and Neck Surgery Foundation published a guideline for the management of AOE. The guideline makes a strong recommendation that clinicians should not prescribe oral antibiotics as initial therapy for diffuse, uncomplicated AOE unless there is extension outside the ear canal or specific factors that would indicate a need for systemic therapy. Instead, the guideline recommends clinicians use topical antibiotic preparations for initial therapy in these cases. If the patient fails to respond to the initial therapy within 48 to 72 hours, the patient should be reassessed. The guideline recognizes there are no significant differences in clinical outcomes of AOE for ototopical antiseptic versus ototopical antibiotic, ototopical quinolone antibiotic versus ototopical non-quinolone antibiotic, or ototopical antibiotic/corticosteroid combination versus antibiotic alone. Regardless of ototopical agent used, about 65% to 90% of patients have clinical resolution within 7 to 10 days.1

Total aggregate quality of evidence was graded as a “B” [Evidence is based on RCTs or overwhelmingly consistent evidence from observational studies], with high level of confidence in the evidence based on RCTs with minor limitations but no direct comparisons of ototopical versus oral antibiotic therapy for AOE. The benefit of using ototopical antibiotics is the avoidance of side effects and reduction in risk for antibiotic resistance. The recommendation for initial ototopical therapy applies to the otherwise healthy patient with diffuse AOE that is not complicated by osteitis, abscess formation, middle ear disease, or recurrent episodes of infection. Topical therapy should be supplemented by oral antibiotics if the patient has a condition, especially diabetes, that is associated with markedly increased morbidity, or immune deficiency that could otherwise impair host defenses; or if the infection has spread beyond the confines of the ear canal into the pinna, skin of the neck or face, or into deeper tissues such as occurs with malignant external otitis.1

The American Academy of Otolaryngology—Head and Neck Surgery Foundation also published a guideline for management of tympanostomy tubes in children. The guideline makes strong recommendations to clinicians to prescribe an ototopical antibiotic only, without oral antibiotics, for children with tympanostomy tubes with acute uncomplicated otorrhea. In these cases, there is discharge from the middle ear through the tube, usually caused by AOM or external contamination of the middle ear from water entry (swimming, bathing, or hair washing). As mentioned already, ototopical antibiotic therapy avoids adverse events associated with systemic antibiotics and mitigates risk for antibiotic resistance. Only ototopical ofloxacin or ciprofloxacin-dexamethasone products are approved for use with tympanostomy tubes. Aminoglycoside-containing eardrops (e.g., containing neomycin), which are used to treat acute otitis externa,
should be avoided in these patients due to increased risk of ototoxicity. Prolonged or frequent use of ototopical quinolone antibiotics may induce fungal external otitis so therapy should be limited to a single course of no more than 10 days.³

Total aggregate quality of evidence was graded as a “B” [Evidence is based on RCTs or overwhelmingly consistent evidence from observational studies], with high level of confidence in the evidence based on RCTs demonstrating equal efficacy of ototopical versus oral antibiotic therapy for otorrhea as well as improved outcomes with ototopical antibiotic therapy when different topical preparations are compared. The benefits of using ototopical antibiotics include increased efficacy by covering common pathogens, including *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA), and avoidance of unnecessary overuse and adverse effects associated with oral antibiotics. Exceptions when systemic antibiotics are indicated include children with complicated otorrhea, cellulitis of adjacent skin, concurrent bacterial infection requiring oral antibiotics (e.g., bacterial sinusitis, group A strep throat), or children who are immunocompromised.³

The American Academy of Pediatrics published a clinical practice guideline on the diagnosis and management of AOM. The guideline does not specifically state ototopical antibiotic preparations as a viable treatment option and these products are not recommended for AOM except in cases when a tympanostomy tube is present.²

**New Safety Alerts:**
None identified.

**New Formulations or Indications:**
Xtoro (finafloxacin 0.3% otic suspension) for ototopical administration was approved by the FDA in December 2014 for the treatment of AOE caused by susceptible strains of *P. aeruginosa* and *S. aureus*.⁴

**Randomized Controlled Trials:**
Fourteen clinical trials were evaluated from the literature search. After further review, no studies were eligible because they did not specifically evaluate formulations currently available in the U.S.
NEW DRUG EVALUATION:
Xtoro (finafloxacin 0.3% otic suspension)

See Appendix 2 for Highlights of Prescribing Information from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations, if applicable.

Clinical Efficacy:
Two unpublished, multi-centered, double-masked, vehicle-controlled, randomized parallel-group studies were conducted and reviewed by the FDA for approval to treat AOE. A total of 686 (age range 11 months to 84 years) and 548 patients (age range 2 to 82 years) were randomized and treated at multiple centers across U.S., Canada and Puerto Rico in studies C-10-018 and C-10-19, respectively. Four drops of finafloxacin or vehicle were applied twice daily in the affected ear(s) for 7 days. The primary efficacy endpoint in these studies was the proportion of patients who achieved clinical cure at Day 11. A clinical cure was attained if the sum of the numerical scores for the signs and symptoms of AOE (tenderness, erythema and edema) was 0 at Day 11 (method of scoring was not specifically defined). The primary efficacy analysis was the pathogen positive subset of the ITT population which included all patients who received study medication and had cultures positive for *P. aeruginosa* and/or *S. aureus* at baseline in the study ear. In C-10-018, 283 patients (41.2%) were included in the ITT pathogen positive subset and in C-10-109, 277 patients (50.5%) were included. Of these patients, 72.3% were positive with *P. aeruginosa* and 27.7% were positive for *S. aureus* isolates. Results in Table 1 show there was a statistically significant difference in clinical cure rates of finafloxacin in both trials compared to placebo vehicle in these patients. Median days till cessation of ear pain was also statistically shorter for finafloxacin compared to placebo vehicle (4.0 days vs. 7.0 days for C-10-18 and 3.0 days vs. 6.5 days for C-10-19, respectively; *p* <0.0001 for both). The FDA found these results to be clinically significant in this population.5

Table 1. Clinical Cure Rates of Acute Otitis Externa at Day 11 in Patients Positive for Bacterial Pathogens in Studies C-10-18 and C-10-19.5

<table>
<thead>
<tr>
<th>Study</th>
<th>Finafloxacin</th>
<th>Placebo Vehicle</th>
<th>Difference</th>
<th>(95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-10-18</td>
<td>104/145 (72%)</td>
<td>46/138 (33%)</td>
<td>38.4%</td>
<td>(27.6 to 49.1%) P &lt;0.0001</td>
</tr>
<tr>
<td>Clinical Cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study C-10-19</td>
<td>Finafloxacin</td>
<td>Placebo Vehicle</td>
<td>Difference</td>
<td>(95% CI) P-value</td>
</tr>
<tr>
<td>Clinical Cure</td>
<td>101/147 (69%)</td>
<td>52/130 (40%)</td>
<td>28.4%</td>
<td>(17.4 to 40.0%) P &lt;0.0001</td>
</tr>
</tbody>
</table>

An evidence table was not created for these studies due to lack of information concerning study methodologies and data analyses.

Author: A. Gibler, Pharm.D. 
Date: May 2015
Clinical Safety:
Finafloxacin was well tolerated on both studies. Attrition due to adverse events was lower for patients receiving finafloxacin compared to placebo in Study C-10-18 (1.7% vs. 4.3%, respectively) but not in Study C-10-18 (4.4% vs. 2.5%, respectively). Discontinuation due to treatment failure was more common in patients receiving placebo vehicle in both studies.

Table 2. Overall Frequency and Incidence of Adverse Events Occurring at Rates of At Least 1.0% in Studies C-10-18 and C-10-19.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Finafloxacin (n=618)</th>
<th>Placebo Vehicle (n=616)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ear Discomfort</td>
<td>2 (0.3%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Ear Pain</td>
<td>3 (0.5%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Ear Pruritus</td>
<td>8 (1.3%)</td>
<td>6 (1.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (1.8%)</td>
<td>18 (2.9%)</td>
</tr>
<tr>
<td>Otitis Media</td>
<td>8 (1.3%)</td>
<td>14 (2.3%)</td>
</tr>
<tr>
<td>Otitis Externa</td>
<td>11 (1.8%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (1.1%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

Look-alike / Sound-alike Error Risk Potential: none

Pharmacology and Pharmacokinetic Properties:

Table 2. Pharmacological Properties of Finafloxacin.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Inhibits DNA gyrase and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>Ototopical doses yielded quantifiable concentrations in 2 of 36 patients with acute otitis externa.</td>
</tr>
</tbody>
</table>
References:
4. Xtoro (finafloxacin otic suspension) 0.3% [prescribing information]. Fort Worth, TX: Alcon Laboratories, Inc., Nov 2014.

Appendix 1: Current Status on Preferred Drug List

<table>
<thead>
<tr>
<th>Preferred Otic Antibiotics</th>
<th>Non-preferred Otic Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLISTIN SULFATE/NEOMYCIN SULFATE/THONZONIUM BROMIDE/HYDROCORTISONE ACETATE SUSP</td>
<td>CIPROFLOXACIN SOL 0.2%</td>
</tr>
<tr>
<td>OFLOXACIN SOL 0.3%</td>
<td>CIPROFLOXACIN/DEXAMETHASONE SUSP 0.3%/0.1%</td>
</tr>
<tr>
<td>NEOMYCIN/POLYMYXIN B/HYDROCORTISONE SUSP 3.5 mg per mL / 10,000 units per mL / 1%</td>
<td>CIPROFLOXACIN/HYDROCORTISONE SUSP 0.2%/1%</td>
</tr>
<tr>
<td></td>
<td>NEOMYCIN/POLYMYXIN B/HYDROCORTISONE SOL 3.5 mg per mL / 10,000 units per mL / 1%</td>
</tr>
</tbody>
</table>
Appendix 2: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all of the information needed to use XTORO safety and effectively. See full prescribing information for XTORO.*

XTORO (finafloxacin otic suspension) 0.3%
For topical otic administration
Initial U.S. Approval: 2014

INDICATIONS AND USAGE
XTORO* is a quinolone antimicrobial indicated for the treatment of acute otitis externa (AOE) caused by susceptible strains of Pseudomonas aeruginosa and Staphylococcus aureus. (1)

DOSAGE AND ADMINISTRATION
Instill four drops in the affected ear(s) twice daily for seven days. For patients requiring use of an otowick, the initial dose can be doubled (to 8 drops), followed by 4 drops instilled into the affected ear twice daily for seven days. (2)

DOSE FORMS AND STRENGTHS
5 mL of finafloxacin otic suspension, 0.3% in 8 mL bottle. (3)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
Prolonged use of this product may lead to overgrowth of nonsusceptible organisms. Discontinue use if this occurs. (5.1)
Allergic reactions may occur in patients with a history of hypersensitivity to finafloxacin, to other quinolones, or to any of the components in this medication. Discontinue use if this occurs. (5.2)

ADVERSE REACTIONS
The most common adverse reactions occurring in 1% of patients with XTORO were ear pruritus and nausea. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. at 1-800-757-9785 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

Revised: 11/2014

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 2 2015

1 exp Otitis Media/ 9195
2 exp Otitis Externa/ 873
3 otic.mp. 1676
4 exp Administration, Topical/ or ototopical.mp. 46643
5 drops.mp. 8833
6 suspension.mp. or exp Suspensions/ 31690
7 exp Solutions/ or solution.mp. 248099
8 neomycin.mp. 3932
9 exp Ciprofloxacin/ 7184
10 exp Ofloxacin/ 4129
11 finafloxacin.mp. 9
12 1 or 2 9937
13 3 or 4 or 5 or 6 or 7 325457
14 8 or 9 or 10 or 11 14476
15 12 and 13 and 14 132
16 limit 15 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) 79
17 limit 16 to yr="2010 -Current" 14