

# Drug Class Review

**Otic Antibiotics**

**Otic Corticosteroids**

**Otic Antibiotic/Corticosteroid Combination Agents**

*52:08.08 Corticosteroids (EENT)*

*52:04.04 Antibacterials (EENT)*

Ciprofloxacin (Cetrazal ®)

Ciprofloxacin/Dexamethasone (Ciprodex ® Otic)

Ciprofloxacin/Hydrocortisone (Cipro HC® Otic)

Dexamethasone

Fluocinolone (DermOtic®)

Neomycin/Colistin/Hydrocortisone/Thonzonium (Coly-mycin®)

Neomycin/Polymyxin B/Hydrocortisone (Cortisporin®)

Ofloxacin (Floxin® Otic)

**Final Report**

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## Table of Contents

Executive Summary.....	3
Introduction .....	4
<i>Disease Overview</i> .....	4
Table 1. Comparison of Otic Agents .....	6
Pharmacology/Pharmacokinetics.....	8
Methods.....	8
Clinical Efficacy .....	9
How do the otic agents compare with each other for reducing symptoms?.....	9
Patient subgroups.....	10
Adverse Drug Reactions.....	10
How does the safety of the otic agents compare with each other?.....	10
Table 2. Adverse Events Reported in the Product Labeling of Otic Agents.....	11
Summary.....	11
References .....	12

## Executive Summary

**Introduction:** Eight otic agents are currently available for use in the United States: ciprofloxacin, ofloxacin, dexamethasone fluocinolone, ciprofloxacin/dexamethasone, ciprofloxacin/hydrocortisone, neomycin/colistin/hydrocortisone/thonzonium, and neomycin/polymyxin B/hydrocortisone. Otic antibiotic and anti-inflammatory agents are indicated in the treatment of acute otitis media, acute otitis externa, and other steroid-responsive inflammatory conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists.

Approximately 7.5 million prescriptions are written annually for otic medications, totaling \$310 million in sales. Treatment of an ear infection varies depending on symptoms and location of infection. In general, cleansing, warm compresses, and an anti-inflammatory agent may be helpful. Topical antibiotic agents are indicated in the treatment of otitis externa. Otitis media is often treated with watchful-waiting and, if an antibiotic is required, an oral agent is usually recommended.

**Clinical Efficacy:** Very little good quality comparative clinical data is available for evaluation of the otic agents. The available evidence suggests otic antibiotic and combination agents are effective in treating susceptible ear infections including acute otitis media in children with tympanostomy tubes and acute otitis externa. No clinically significant differences in safety or efficacy were found in the majority of the trials comparing an antibiotic agent to an antibiotic/corticosteroid agent.

*Special Populations:* Otic fluoroquinolones and combination agents are approved for use in pediatric patients as young as 6 months old.

**Adverse Drug Reactions:** Adverse events reported with the topical otic agents are related to local irritation upon instillation. The most common drug-related adverse reactions to the otic agents include itching, swelling, and headache. Aminoglycoside agents should not be used in patients with a perforated tympanic membrane. Corticosteroid agents should not be used in patients with viral infections involving the external ear canal.

**Summary:** Infections of the ear can be painful, lead to lost work/school days and, in severe cases, lead to hearing loss. Otic antibiotic agents are used to treat or prevent an infection and, when combined with a corticosteroid agent, may work to reduce inflammation associated with the infection. The available evidence suggests otic antibiotic and combination agents are effective in treating acute otitis media in children with tympanostomy tubes and acute otitis externa.

## Introduction

Otic antibiotic and anti-inflammatory agents may be used for a number of ear conditions, including treatment of acute otitis media, acute otitis externa, and other steroid-responsive inflammatory conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists.<sup>1-3</sup> A total of eight otic agents are currently available for use in the United States: two antibiotic agents (ciprofloxacin and ofloxacin), two anti-inflammatory agents (dexamethasone and fluocinolone), and four combination agents (ciprofloxacin/dexamethasone, ciprofloxacin/hydrocortisone, neomycin/colistin/hydrocortisone/thonzonium, and neomycin/polymyxin B/hydrocortisone).<sup>1,2</sup> Table one compares the available otic agents.

### *Disease Overview*

An ear infection is characterized by swelling, redness and pain of the middle or outer ear.<sup>3</sup> The infection may be caused by a bacteria, virus, or, in rare cases, fungus.<sup>3,4</sup> Approximately 2.4 million visits to healthcare clinics and emergency rooms and over half a billion in direct healthcare costs were a result of outer ear infections in 2007.<sup>4,5</sup> Another 25 million office visits annually and \$3 billion in direct care health care costs are a result of middle ear infections. When lost wages for parents are included, the total cost reaches \$6 billion. In total, approximately 7.5 million prescriptions are written annually for otic medications totaling \$310 million in sales.<sup>4,5</sup>

Infections of the ear may involve parts of the middle ear and/or the outer ear, including the skin, cartilage, ear canal, and tympanic/mastoid cavities.<sup>3</sup> Clinical manifestations of an ear infection may include tenderness, erythema, swelling, itching and discharge. Infections of the outer ear can be difficult to distinguish from noninfectious inflammatory conditions because they have similar signs and symptoms. Auricular cellulitis, perichondritis, and otitis externa are examples of infections of the outer ear. Auricular cellulitis is an infection of the skin overlying the external ear and often results from local trauma. Perichondritis is an infection of the connective tissue surrounding the auricular cartilage and may also follow local trauma. Otitis externa refers to a group of infections of the auditory opening, usually resulting from a combination of heat and moisture. Otitis externa can be localized (furunculosis), diffuse (swimmer's ear), chronic (caused by repeated local irritation), or invasive (malignant or necrotizing otitis externa). Otitis media is a condition of the middle ear involving an inflammatory response and the development of sterile transudate. It usually occurs along with an upper respiratory infection as a result of eustachian tube dysfunction.<sup>3</sup>

Treatment of an ear infection varies depending on symptoms and location of infection.<sup>3</sup> In general, cleansing, warm compresses, and an anti-inflammatory agent may be helpful. An antibiotic against typical skin and soft tissue pathogens (i.e. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *streptococci*) may be required if a bacterial infection is present. Topical antibiotics are usually indicated in the treatment of "swimmers ear" and oral antibiotics are required for auricular cellulitis or perichondritis. Otitis media is often treated with watchful-waiting; an oral antibiotic may be required in cases where the condition does not improve or resolve with time.<sup>3</sup> Guidelines by the American Academy of Otolaryngology-Head and Neck Surgery Foundation (AAO-HNSF)<sup>6</sup> recommend the use of a topical otic agent in the treatment of

uncomplicated cases of otitis externa. According to the guidelines, a specific first-line agent is not recommended but the ciprofloxacin/hydrocortisone (Cipro HC® Otic) combination product may be associated with less pain and steroid-containing agents may be associated with less itching. Guidelines by the American Academy of Pediatrics and the American Academy of Family Physicians (AAP/AAFP)<sup>7, 8</sup> do not recommend antibiotic or corticosteroid use in the treatment of otitis media. However, if an antibiotic is required, amoxicillin should be used as first line treatment. Of note, ciprofloxacin/dexamethasone (Ciprodex ® Otic) has an indication for use in patients with otitis media who also have tympanostomy tubes.

**Table 1. Comparison of Otic Agents<sup>1,2</sup>**

Product	Drug class	Available formulations	Preservative in product	Labeled uses	Dose Range, Adults	Age range	Generic Available
<b>Ciprofloxacin (Cetraxal®)</b>	Antibiotic	Otic solution, as hydrochloride: 0.5 mg/0.25 mL [equivalent to ciprofloxacin base 0.2%]	preservative-free	Treatment of acute otitis externa due to susceptible strains of <i>Pseudomonas aeruginosa</i> or <i>Staphylococcus aureus</i>	Instill 1 drop into affected ear twice daily for 7 days	Children ≥1 year	Limited availability
<b>Ciprofloxacin/Dexamethasone (Ciprodex®)</b>	Antibiotic/Corticosteroid combination	Otic suspension: Ciprofloxacin 0.3% and dexamethasone 0.1% (7.5 mL)	benzalkonium chloride	Treatment of acute otitis media in pediatric patients with tympanostomy tubes or acute otitis externa in children and adults	Instill 4 drops into affected ear(s) twice daily for 7 days	Children ≥ 6 months	No; 8/2020
<b>Ciprofloxacin/Hydrocortisone (Cipro® HC)</b>	Antibiotic/Corticosteroid combination	Otic suspension: Ciprofloxacin hydrochloride 0.2% and hydrocortisone 1% (10 mL)	benzyl alcohol	Treatment of acute otitis externa, sometimes known as “swimmer's ear”	Instill 3 drops of the suspension in the affected ear twice daily for 7 days	Children ≥1 year	No; 6/2015
<b>Dexamethasone</b>	Corticosteroid	<b>Ophthalmic</b> solution: 0.1% (5 mL)	benzalkonium chloride	The ophthalmic solution is indicated for otic use to treat steroid-responsive inflammatory conditions of the external auditory meatus.	Instill 3-4 drops into the aural canal 2-3 times a day	Not specified	Yes
<b>Fluocinolone (DermOtic®)</b>	Corticosteroid	Otic oil: 0.01% (20 mL) *contains peanut oil	preservative-free *contains peanut oil	Relief of chronic eczematous external otitis	5 drops into the affected ear twice daily for 1-2 weeks	Children ≥2 years	Yes
<b>Neomycin/Colistin/Hydrocortisone/Thonzonium (Coly-Mycin® S; Cortisporin®-TC)</b>	Antibiotic/Corticosteroid combination	Otic suspension: Neomycin 0.33%, colistin 0.3%, hydrocortisone acetate 1%, and thonzonium bromide 0.05% (5 mL, 10 mL)	thimerosal	Treatment of superficial and susceptible bacterial infections of the external auditory canal; for treatment of susceptible bacterial infections of mastoidectomy and fenestration cavities	4-5 drops in affected ear 3-4 times/day	Children ≥1 year	Limited availability

<b>Neomycin/Polymyxin B/Hydrocortisone (Cortisporin®; Cortomycin)</b>	Antibiotic/Corticosteroid combination	Otic solution: Neomycin 3.5 mg, polymyxin B 10,000 units, and hydrocortisone 10 mg per 1 mL (10 mL)  Otic suspension: Neomycin 3.5 mg, polymyxin B 10,000 units, and hydrocortisone 10 mg per 1 mL (10 mL)	potassium metabisulfite	Steroid-responsive inflammatory condition for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial infection exists	Instill 1-3 drops 2-4 times/day	Children ≥2 years	Yes
<b>Ofloxacin (Floxin®)</b>	Antibiotic	Otic solution: 0.3% (5 mL, 10 mL)	benzalkonium chloride	Otitis externa, chronic suppurative otitis media, acute otitis media	Instill 5 drops 1-2 times/day	Children ≥ 6 months	Yes

## **Pharmacology/Pharmacokinetics<sup>1-3</sup>**

Topical application of the otic agents increases drug concentrations at the site of infection, minimizes systemic absorption, reduces the risk of antibiotic resistance and eliminated the potential for antibiotic resistance.

### Antibiotics.

Ciprofloxacin is a fluoroquinolone antibiotic. Fluoroquinolone antibiotics inhibit bacterial deoxyribonucleic acid (DNA) replication, repair, deactivation, and transcription by directly inhibiting the DNA gyrase enzyme. Ciprofloxacin has a wide-range of gram-negative and gram-positive antimicrobial activity but may have better activity against gram-negative bacilli than other fluoroquinolones.

Colistin is a polymyxin antibiotic. Polymyxin antibiotics work by increasing the permeability of bacterial cell membranes. Colistin exhibits bactericidal action against most gram-negative organisms, including *P. aeruginosa*, *Eschericia coli*, and *Klebsiella-Aerobacter sp.*

Neomycin is an aminoglycoside antibiotic. Aminoglycoside antibiotics interfere with bacterial protein synthesis. More specifically, neomycin irreversibly binds to the 30S subunit of bacterial ribosomes, blocking the recognition step in protein synthesis and causing misreading of the genetic code. Neomycin exhibits bactericidal action against most pathogens, including *S. aureus* and *Proteus sp.*

Like ciprofloxacin, ofloxacin is a fluoroquinolone antibiotic. Ofloxacin also has a wide-range of gram-negative and gram-positive antimicrobial activity but may have a longer half-life than ciprofloxacin.

Like colistin, polymyxin B interferes with bacterial cell membrane permeability. Polymyxin B is bactericidal against nearly all gram-negative bacilli except the *Proteus* group.

### Corticosteroids.

Corticosteroids form steroid-receptor complexes which bind to DNA and result in stimulation of the production of a glycoprotein which inhibits the activity of inflammatory mediators. Hydrocortisone and dexamethasone are corticosteroid agents used to control inflammation, edema, pruritus, and other dermal reactions.

### Other.

Thonzonium bromide is a surface-active detergent that increases tissue contact of the otic agent by dispersion of cellular exudate and debris.

## **Methods**

A literature search was conducted to identify articles addressing each key question, searching the MEDLINE database (1950 – 2012), the Cochrane Library, and

reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE prior to 12/2012, evaluating efficacy of the corticosteroid and antibiotic otic agents with reduction of symptoms or cure as the endpoint are included. Trials evaluating the otic agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded. Due to the differences in international bacterial susceptibility, only studies performed in the United States were considered. The following reports were excluded (note: some were excluded for more than 1 reason):

- Individual clinical trials which evaluated endpoints other than reduction of symptoms, such as pharmacokinetic studies<sup>9, 10</sup>, or cost analysis.<sup>11, 12</sup>
- Individual trials comparing the otic agents in dose-finding studies or in healthy volunteers.
- Individual clinical trials evaluating the otic agents or formulations not currently available in the US<sup>13</sup> or clinical trials without access to the full article.<sup>14</sup>

## **Clinical Efficacy**

Very little good quality comparative clinical data is available for evaluation of the otic agents. Overall, no trials comparing the two otic antibiotics or two otic corticosteroids are available for evaluation. Only one trial comparing the combination products is available for evaluation.<sup>15</sup> No meta-analyses evaluating comparative trials are available for evaluation of the otic agents. Of note, four trials<sup>16-20</sup> comparing combination products to single-agent products are available for evaluation. A summary of these trials is included below.

- **How do the otic agents compare with each other for reducing symptoms?**

One randomized, controlled trial evaluated the efficacy of ciprofloxacin/dexamethasone and neomycin/polymyxin B/hydrocortisone in 468 patients over one year of age with acute otitis externa.<sup>15</sup> Patients were randomized to receive ciprofloxacin 0.3%/dexamethasone 0.1% suspension twice daily or neomycin 0.35%/polymyxin B 10,000 IU/mL/hydrocortisone 1% otic suspension three times daily for 7 days. Clinical cure rate was reported in 90.9% of patients in the ciprofloxacin/dexamethasone group compared to 83.9% of the patients in the neomycin group (p=0.0375). Microbiological cure rates were also significantly higher in the ciprofloxacin/dexamethasone group (94.7% vs. 86%; p=0.0057). No differences in adverse events were reported between treatment groups.

Four clinical trials compared single-agent products to combination agents. One multicenter trial evaluated the efficacy of ciprofloxacin/dexamethasone and ofloxacin in 599 children (aged 6mo-12yr) with acute otitis media with tympanostomy tubes.<sup>19</sup> Clinical and microbial cure rates were better in the ciprofloxacin/dexamethasone group compared to the ofloxacin group (p < 0.05). A second multicenter trial compared

ciprofloxacin 0.2% to neomycin/polymyxin B/hydrocortisone in 630 patients with acute otitis externa.<sup>16</sup> Ciprofloxacin was found to be non-inferior to neomycin/polymyxin B/hydrocortisone in the treatment of otitis externa. Two trials comparing ofloxacin to neomycin/polymyxin B/hydrocortisone in adults and children demonstrated no differences clinical cure rates between treatment groups.<sup>17, 20</sup> No differences in adverse event rates were reported in any of the trials.

Overall, the available evidence suggests otic antibiotic and combination agents are effective in treating susceptible ear infections including acute otitis media in children with tympanostomy tubes and acute otitis externa. No clinically significant differences in safety or efficacy were found in the majority of the trials comparing an antibiotic agent to an antibiotic/corticosteroid agent. This evidence suggests the addition of a corticosteroid may be unnecessary.

- **Are there patient subgroups based on demographics (e.g., age, racial groups, gender) or comorbidities for which one of the otic agents is more effective or associated with fewer adverse effects?**

#### *Pediatrics*<sup>1, 2</sup>

Otic fluoroquinolones and combination agents are approved for use in pediatric patients; however the age is not always specified. Some of the agents are approved for use in children as young as six months old. See table one for a summary of approved indications and age restrictions for each of the otic agents.

#### **Adverse Drug Reactions**

- **How does the safety of the otic agents compare with each other?**

Adverse events reported with the topical otic agents are related to local irritation upon instillation.<sup>1-3</sup> See table two for a summary of adverse events associated with the otic agents. The most common drug-related adverse reactions to the otic agents include itching, swelling, and headache; however, these symptoms may also be signs/symptoms of the ear condition. Ototoxicity and hearing loss may occur with the aminoglycoside/steroid combination agents (i.e. neomycin, polymyxin B, and hydrocortisone) in the case of a perforated tympanic membrane and these agents should not be used in patients with suspected perforated membrane. Fluoroquinolones are not associated with ototoxicity and may be used in patients with a perforated tympanic membrane. Corticosteroid and neomycin containing products should not be used in viral infections involving the external ear canal such as varicella or herpes simplex.<sup>1-3</sup>

**Table 2. Adverse Events Reported in the Product Labeling of Otic Agents<sup>1,2</sup>**

Agent	Local adverse events (%)			Systemic adverse events (%)			
	Application site reactions	Pain	Pruritus	Dizziness	Headache	Ototoxicity	Vertigo
<b>Ciprofloxacin (Cetraxal®)</b>	NR	2-3	2-3	NR	2-3	NR	NR
<b>Ciprofloxacin/Dexamethasone (Ciprodex®)</b>	NR	0.4	1.5	NR	NR	NR	NR
<b>Ciprofloxacin/Hydrocortisone (Cipro® HC)</b>	NR	NR	0.4	NR	1.2	NR	NR
<b>Dexamethasone</b>	NR	NR	NR	NR	4	NR	NR
<b>Fluocinolone (DermOtic®)</b>	NR	NR	NR	NR	NR	NR	NR
<b>Neomycin/Colistin/Hydrocortisone/Thonzonium (Coly-Mycin® S; Cortisporin®-TC)</b>	reported	NR	reported	NR	NR	reported	NR
<b>Neomycin/Polymyxin B/Hydrocortisone (Cortisporin®; Cortomycin)</b>	reported	NR	reported	NR	NR	reported	NR
<b>Ofloxacin (Floxin®)</b>	3-16.8	<1	1.2-4	1	0.3	NR	1

Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. NR = not reported.

## Summary

Infections of the ear can be painful, lead to lost work/school days and, in severe cases, lead to hearing loss. Otic antibiotic agents are used to treat or prevent an infection and, when combined with a corticosteroid agent, may work to reduce inflammation associated with the infection. Eight topical otic agents are currently available for use in the United States: two antibiotic agents, two corticosteroid agents, and four combination products. Very little quality comparative evidence is available for evaluation of the otic agents. The available evidence suggests otic antibiotic and combination agents are effective in treating acute otitis media in children with tympanostomy tubes and acute otitis externa. Aminoglycoside-containing agents should not be used in patients with a suspected or known perforated tympanic membrane. Corticosteroid-containing agents should not be used in patients with viral infections involving the external ear canal. Overall, there are not enough published comparative trials to distinguish any of the available otic products from the others.

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