# *Otic Antibiotics Review*

*12/15/2009*



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## *FDA-Approved Indications*

| Drug Name | Manufacturer | Indication(s) |
|---|---|---|
| ciprofloxacin 0.2% (Cetraxal®) | Wraser Pharmaceuticals | • Acute otitis externa due to susceptible isolates of *Pseudomonas aeruginosa* or *Staphylococcus aureus* in pediatrics (age one year and older) and adults |
| ciprofloxacin 0.3% and dexamethasone 0.1% suspension (Ciprodex® Otic)[1] | Alcon | • Acute otitis media in pediatric patients (age six months and older) with tympanostomy tubes<br>• Acute otitis externa in pediatric (age six months and older), adult, and elderly patients |
| ciprofloxacin 0.2% and hydrocortisone 1% suspension (Cipro HC® Otic)[2] | Alcon | • Acute otitis externa in adult and pediatric patients, (one year and older) |
| 1% hydrocortisone, 3.3 mg neomycin sulfate, 3 mg colistin sulfate, 0.05% thonzonium bromide suspension (Coly-mycin® S)[3] | JHP Pharmaceuticals | • Treatment of superficial bacterial infections of the external auditory canal in adult and pediatric patients*<br>• Treatment of infections of mastoidectomy and fenestration cavities in adult and pediatric patients* |
| 1% hydrocortisone, 5 mg neomycin sulfate, 10,000 units polymyxin B solution and suspension (Cortisporin®)[4] | generics | • Treatment of superficial bacterial infections of the external auditory canal in adults and pediatric patients ( 2 years and older)<br>• Treatment of infections of mastoidectomy and fenestration cavities (suspension only) in adults and pediatric patients ( 2 years and older) |
| 1% hydrocortisone, 3.3 mg neomycin sulfate, 3 mg colistin sulfate, 0.05 mg thonzonium Br suspension (Cortisporin®-TC)[5] | JHP Pharmaceuticals | • Treatment of superficial bacterial infections of the external auditory canal in adult and pediatric patients*<br>• Treatment of infections of mastoidectomy and fenestration cavities in adult and pediatric patients* |
| ofloxacin 0.3% solution (Floxin® Otic)[6] | generic | • Otitis externa in adults and pediatric patients (six months and older)<br>• Chronic suppurative otitis media in patients 12 years and older with perforated tympanic membranes<br>• Acute otitis media in pediatric patients (one year and older) with tympanostomy tubes |

***** Specific pediatric age not listed in package insert.

## *Overview*[7,8,9,10]

The standard treatment for acute otitis media (AOM) has been the use of systemic antibiotics while topical (otic) therapy antibiotic is generally used for otitis externa. Topical antibiotics such as ofloxacin (Floxin Otic) and ciprofloxacin with dexamethasone (Ciprodex) may help to decrease adverse reactions and reduce the potential for antibiotic resistance when used in patients with AOM and with tympanostomy tubes. The patent tympanostomy tube does not change the spectrum of causative agents in acute otitis media.

Otitis externa is an acute inflammation of the external auditory canal. Commonly referred to as "swimmer's ear" or "tropical ear", this condition is often precipitated by water exposure or trauma. Common pathogens implicated in otitis externa are *Pseudomonas aeruginosa and Staphylococcus aureus,* often occurring as a polymicrobial infection. Patients will typically complain of otalgia and otorrhea, and the ear canal may appear erythematous and swollen. It is imperative that the ear canal be cleared of any discharge or debris that can occlude the canal since the presence of such material can keep the canal moist and interfere with topical treatment. All ages are affected, with a peak incidence in children aged seven to 12 years. In 2006, The American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) released guidelines for the management of acute otitis externa (AOE) in patients over two years of age.[11] Clinicians should use topical preparations for initial therapy of diffuse, uncomplicated AOE. Systemic antimicrobial therapy should not be used unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy. A topical aminoglycoside combined with a second antibiotic and a topical steroid such as neomycin, polymyxin B, and hydrocortisone is commonly prescribed to treat AOE. However, caution must be used to watch for a hypersensitivity reaction to the neomycin and ototoxicity from the aminoglycoside. This preparation should not be used in cases of a perforated tympanic membrane. However, if the tympanic membrane is known or suspected to be perforated, agents with ototoxic potential, such as aminoglycosides, should not be used. Fluoroquinolones are not associated with ototoxicity, and ofloxacin is safe in cases of a perforated tympanic membrane. If the patient fails to respond to the initial therapeutic option within 48 to 72 hours, the clinician should reassess the patient to confirm the diagnosis of diffuse AOE and to exclude other causes of illness.

Clinical Practice Guidelines for acute otitis media (AOM) were released in 2004 by the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP). The guidelines recommend an observatory period instead of prescribing an antibiotic. When an antibiotic is needed, amoxicillin is the first line treatment. Other antibiotic choices should be based on clinical experience and type of organism present. No specific recommendation for use of topical antibiotics was included in these guidelines.[12]

Chronic suppurative otitis media (CSOM) defined as a perforated tympanic membrane with persistent drainage from the middle ear and initiated by an episode of acute infection. *P. aeruginosa* is the most common causative organism followed by *S. aureus*. The yearly incidence of CSOM is estimated to be 39 cases per 100,000 persons in children and adolescents aged 15 years and younger in the United States. CSOM responds more frequently to topical than to systemic therapy. Successful topical therapy includes administration of antibiotic drops and aural irrigation. The antibiotic should have activity against both gram-negative and gram-positive organisms. Aminoglycosides and fluoroquinolones both have spectrum of activity against gram-negative and gram-positive organisms, However, aminoglycosides may potentially be ototoxic and therefore are not recommended to be used if the tympanic membrane is perforated.[13]

## *Pharmacology*

Ofloxacin and ciprofloxacin are fluoroquinolones and have activity against a wide range of gram-negative and gram-positive microorganisms. Fluoroquinolones act by inhibiting the DNA gyrase enzyme that is essential for DNA replication, repair, deactivation, and transcription.

Hydrocortisone and dexamethasone are corticosteroids that control inflammation, edema, pruritus, and other dermal reactions.

Colistin sulfate is an antibiotic with bactericidal action against most gram-negative organisms, notably *P. aeruginosa, Eschericia coli,* and *Klebsiella-Aerobacter* sp.

Neomycin sulfate is an aminoglycoside and broad-spectrum antibiotic that is bactericidal to many pathogens, notably *S. aureus* and *Proteus* sp. Neomycin irreversibly binds to the 30S subunit of bacterial ribosomes, blocking the recognition step in protein synthesis and causing misreading of the genetic code.

Polymyxin B increases the permeability of bacterial cell membranes and is bactericidal against almost all gram-negative bacilli except the *Proteus* group.

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

It is thought that because topical application establishes and maintains drug concentrations at the site of infection that are well above the minimum inhibitory concentration, resistance is not likely to develop following topical use. A systematic review of the evidence regarding the development of antibiotic resistance with ototopical treatment indicated that antibiotic resistance is rare, although in none of the studies was resistance the main study question.[14,15,16]

## *Pharmacokinetics*

Due to the topical application of these products, minimal systemic absorption is expected.[17]

Ciprofloxacin (Cetraxal): After administration of 0.25 mL of Cetraxal, plasma concentrations were not measurable (total dose: 0.5 mg ciprofloxacin). The maximum plasma concentration is less than 5 ng/mL.[18]

Ofloxacin (Floxin Otic): The concentration of ofloxacin in middle ear fluid is variable based on the patient's disease state. Serum ofloxacin concentrations were low in patients with tympanostomy tubes and/or perforated tympanic membranes.[19]

Ciprofloxacin/dexamethasone (Ciprodex): Both ciprofloxacin and dexamethasone appear in the plasma at measurable concentrations although the concentrations are approximately 0.1 percent and 14 percent, respectively, of an oral dose of ciprofloxacin 250 mg tablet and dexamethasone 0.5 mg tablet.[20] Peak plasma concentrations for both components were seen between 15 minutes and 2 hours after dose application.

Ciprofloxacin/hydrocortisone (Cipro HC): Ciprofloxacin concentrations in the blood are expected to be below the level of detection, and therefore have not been measured. Levels of hydrocortisone are not distinguishable from naturally occurring levels.[21]

### *Contraindications/Warnings*[22,23,24,25,26,27,28]

Corticosteroid and neomycin containing products should not be used in viral infections involving the external ear canal such as varicella and herpes simplex.

Neomycin may induce permanent sensorineural hearing loss due to cochlear damage. Neomycin containing products should be used cautiously in any patient with a perforated tympanic membrane. It may also cause cutaneous sensitization.

Ciprodex Otic and Floxin Otic are both sterile products. Cipro HC Otic is a non-sterile product and should not be used if the tympanic membrane is perforated.

Cipro HC and Ciprodex Otic are contraindicated in patients with a history of hypersensitivity to ciprofloxacin, quinolones or other components, (i.e. dexamethasone or hydrocortisone), of these product. Ofloxacin Otic is contraindicated in patients with a history of hypersensitivity to ofloxacin, other quinolones or any components of this product. Ciprofloxacin otic is contraindicated in patients with ciprofloxacin hypersensitivity.

None of the products included in this review are approved for ophthalmic use, inhalation, or for injection.

### *Drug Interactions*[29,30,31,32,33,34,35]

Since all agents are applied topically and have negligible systemic absorption; no documented drug interactions are currently available.

## *Adverse Effects*

*Patients with Otitis Externa*

| Drug | Pruritus | Application site reaction | Dizziness | Ear pain/ discomfort | Vertigo | Headache | Ototoxicity |
|---|---|---|---|---|---|---|---|
| ciprofloxacin (Cetraxal)[36] | reported | reported | nr | reported | nr | reported | nr |
| ciprofloxacin/ dexamethasone (Ciprodex Otic)[37] n=537 | 1.5 | nr | nr | 0.4 | nr | nr | nr |
| ciprofloxacin/ hydrocortisone (Cipro HC Otic)[38] n=564 | 0.4 | nr | nr | nr | nr | 1.2 | nr |
| ofloxacin (Floxin Otic)[39] n=229 | 4 | 3 | 1 | 1 | 1 | 0 | nr |
| neomycin/colistin/ thonzonium/HC (Coly-mycin S)[40] | reported | reported | nr | nr | nr | nr | reported |
| neomycin/colistin/ thonzonium/HC (Cortisporin-TC)[41] | reported | reported | nr | nr | nr | nr | reported |
| neomycin/ polymyxin B/HC (Cortisporin)[42] | reported | reported | nr | nr | nr | nr | reported |

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Ciprofloxacin may also be associated with fungal ear superinfection.[43]

## *Adverse Effects (continued)*

*Patients with Acute Otitis Media and Chronic Suppurative Otitis Media*

| Drug | Taste Perversion | Ear pain/ discomfort | Pruritus | Paresthesia | Rash | Dizziness |
|---|---|---|---|---|---|---|
| ciprofloxacin/ dexamethasone (Ciprodex Otic)[44] n=400 | 0.5 | 2.3/3 | reported | nr | nr | reported |
| ofloxacin (Floxin Otic)[45] n=656 | 7 | 1 | 1 | 1 | 1 | 1 |

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Neomycin-containing products[46 47 48]: Neomycin sensitization appears as a low-grade reddening with swelling, dry scaling, and itching; it may be manifest simply as a failure to heal.

Hydrocortisone:[49 50 51] This drug may be associated with the following adverse effects: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

## *Special Populations*[52,53,54,55,56,57,58]

### *Pediatrics*

Otic fluoroquinolones, Coly-mycin S, and Cortisporin TC are approved for use in pediatric patients, however the age is not specified.

Cetraxal and Cipro HC are indicated for use in children one year of age and older.

Cortisporin is approved for use in children two years of age and older.

Floxin Otic and CiproDex are approved for usage in children as young as six months old.

### *Pregnancy*

All agents in this class are Pregnancy Category C.

## *Dosages*

| Drug | Indication | Dose | Duration (days) | Age | Pkg size |
|---|---|---|---|---|---|
| ciprofloxacin (Cetraxal)[59] | Acute Otitis Externa | One single use container affected ear twice daily (approximately 12 hours apart) | 7 | 1 year and older | 14 single use containers (0.25ml) |
| ciprofloxacin/dexamethasone (Ciprodex Otic)[60] | All indications | 4 drops affected ear twice daily | 7 | 6 months and older | 7.5 mL bottle |
| ciprofloxacin/hydrocortisone (Cipro HC Otic)[61] | Otitis Externa | 3 drops affected ear twice daily | 7 | 1 year and older | 10 mL bottle |
| neomycin/colistin/ thonzonium/HC (Coly-mycin S)[62] | All indications | 3 to 4 drops three to four times daily | 10 | Pediatrics* | 5 mL bottle |
| | All indications | 4 to 5 drops three to four times daily | 10 | Adults | |
| neomycin/colistin/ thonzonium/HC (Cortisporin-TC)[63] | All indications | 3 to 4 drops three to four times daily | 10 | Pediatrics* | 10 mL bottle |
| | All indications | 4 to 5 drops three to four times daily | 10 | Adults | |
| neomycin/polymyxin B/HC (Cortisporin)[64] | All indications | 3 drops three to four times daily | 10 | 2 years and older | 10 mL bottle |
| | All indications | 4 drops three to four times daily | 10 | Adults | |
| ofloxacin (Floxin Otic)[65] | Otitis Externa | 5 drops affected ear daily | 7 | 6 mo-12 yr | 5 and 10 mL bottles; 0.25 mL single dose units |
| | Otitis Externa | 10 drops affected ear daily | 7 | 13 years and older | |
| | Acute Otitis Media | 5 drops affected ear twice daily | 10 | 1-12 years | |
| | Chronic Suppurative Otitis Media | 10 drops affected ear twice daily | 14 | 12 years and older | |

***** Specific pediatric age not listed in package insert.

## *Clinical Trials*

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and the FDA-approved indications. Comparative clinical trials have been performed with some of the agents in this class. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Very little comparative literature of good quality is available. Due to the differences in international bacterial susceptibility, only studies performed in the United States were considered. Most studies were performed in a single-masked manner.

ciprofloxacin/dexamethasone (Ciprodex) and ofloxacin (Floxin Otic)

In a multicenter trial of 599 children (ages six months to 12 years) with acute otitis media with otorrhea through tympanostomy tubes (AOMT), patients were randomized to receive either ciprofloxacin/dexamethasone four drops twice daily for seven days or ofloxacin five drops twice daily for ten days.[66] In the observer-masked trial, clinical signs and symptoms of AOMT were evaluated at clinic visits on days one, three, 11, and 18 (test of cure). Pathogens included *Streptococcus pneumoniae* (16.8 percent), *S. aureus* (13 percent), *P. aeruginosa* (12.7 percent), *Haemophilus influenzae* (12.4 percent), *Staphylococcus epidermidis* (10.2 percent), and *Moraxella catarrhalis* (4.1 percent). Clinical cure rates at the test-of-cure visit were better in the ciprofloxacin/dexamethasone group (90 versus 78 percent; p=0.0025). Microbiologic success was 92 percent for the ciprofloxacin/dexamethasone group and 81.8 percent for the ofloxacin group (p=0.0061). Fewer treatment failures were seen with ciprofloxacin/dexamethasone (4.4 percent) than ofloxacin (14.1 percent). Both treatments had similar adverse event profiles.

ciprofloxacin/dexamethasone (Ciprodex) and neomycin/polymyxin B/hydrocortisone

A randomized, observed-masked trial enrolled 468 patients over one year of age with acute otitis externa and intact tympanic membranes to compare the efficacy and safety of seven-day treatment with ciprofloxacin/dexamethasone and neomycin/polymyxin B/hydrocortisone.[67] Patients were randomized to ciprofloxacin 0.3%/dexamethasone 0.1% suspension given as three to four drops twice daily or neomycin 0.35%/polymyxin B 10,000 IU/mL/hydrocortisone 1% otic suspension given as three to four drops three times daily. Patients with positive cultures (n=396) had a clinical cure rate at day 18 of 90.9 percent with the ciprofloxacin/dexamethasone product versus 83.9 percent with the neomycin combination product (p=0.0375). Microbiological cure rates were also significantly higher in the ciprofloxacin/dexamethasone group (94.7 versus 86 percent; p=0.0057). Both treatments were well tolerated.

ciprofloxacin (Cetraxal) and neomycin/polymyxin B/hydrocortisone

Due to a lack of other studies, this observer-blinded study has been included. To compare efficacy and safety, a multicenter, observer-blinded study of 630 patients with acute otitis externa was conducted.[68] Patients were randomized to receive either ciprofloxacin 0.2% twice daily or neomycin/polymyxin B/hydrocortisone otic solution three times daily for seven days. Clinical cure was achieved at the end of a seven-day treatment in 70 percent for the ciprofloxacin-treated group versus 60.5 percent for the neomycin/polymyxin B/hydrocortisone group. Ciprofloxacin was shown to be noninferior to neomycin/polymyxin B/hydrocortisone. The clinical cure rate for patients with baseline cultures showing *P. aeruginosa* was 87.5 percent in the ciprofloxacin group and 78.6 percent in the neomycin/polymyxin B/hydrocortisone group. In patients with baseline cultures showing *S. aureus*, the clinical cure rate was 72.7 percent for the ciprofloxacin group and 75.9 percent for the neomycin/polymyxin B/hydrocortisone group.

ciprofloxacin/hydrocortisone (Cipro HC) and neomycin/polymyxin B/hydrocortisone (Cortisporin) plus systemic amoxicillin

A randomized, multicenter, active-control, observer-blind, non-inferiority trial of 206 adult and children patients with acute otitis externa compared ciprofloxacin/hydrocortisone with neomycin/polymyxin B/hydrocortisone plus systemic amoxicillin for clinical equivalence.[69] Patients received either ciprofloxacin/hydrocortisone otic three drops twice daily for seven days or neomycin/polymyxin B/hydrocortisone two drops (child) or four drops (adult) plus systemic amoxicillin 250 mg three times daily for 10 days. The primary efficacy variable was response to therapy seven days after treatment ended (test of cure). The study demonstrated clinical non-inferiority of ciprofloxacin/hydrocortisone group when compared to neomycin/polymyxin B/hydrocortisone plus amoxicillin. Response to therapy for ciprofloxacin/hydrocortisone was 95.71 percent versus 89.83 percent for neomycin/polymyxin B/hydrocortisone plus amoxicillin. Both groups had a median time to end of pain of six days.

ofloxacin (Floxin Otic) and neomycin/polymyxin B/hydrocortisone (Cortisporin)

Adults and children with otitis externa were randomized to receive ofloxacin otic solution ten drops or five drops twice daily, respectively, or neomycin/polymyxin B/hydrocortisone otic solution four drops or three drops four times daily for ten days.[70] A total of 314 adults and 287 children were enrolled. In the investigator-blinded study, the overall clinical response was a cure rate of 97 percent of ofloxacin-treated children and 95 percent of neomycin combination-treated children (p=NS). The overall clinical response was cure in 82 percent of ofloxacin-treated adults and 84 percent of neomycin combination-treated adults (p=NS). There were no differences in the incidence of any adverse events between treatment arms.

A double-blind study enrolled 52 patients with active chronic suppurative otitis media (CSOM). Patients were randomized to receive treatment for two weeks with either topical ofloxacin or neomycin/polymyxin B/hydrocortisone.[71] At the conclusion of the study, microbiologic eradication was noted in 81 percent and 75 percent of patients, respectively (p=NS). Clinical cure rates were 89 percent for ofloxacin and 79 percent for neomycin/polymyxin B/hydrocortisone (p=NS). In the study, ofloxacin had better coverage against *Staphylococcus aureus* (93 percent versus 68 percent), *Staphylococcus epidermidis* (83 percent versus 73 percent) and *Pseudomonas aeruginosa* (100 percent versus 86 percent). The adverse events were similar in each group.

 

## *Summary*

Otic antibiotics provide an alternative to systemic oral medication in the treatment of acute otitis media in children with tympanostomy tubes and are effective treatments for acute otitis externa.

Since many AOMT patients have received multiple antibiotics prior to getting tympanostomy tube placement, higher rates of antibiotic resistance may be noted in these patients. Due to the high levels of antibiotic achieved, the use of broad spectrum fluoroquinolones may overcome some of the bacterial resistance. While the addition of a corticosteroid may be of benefit in reducing inflammation, some consider the use of corticosteroids unnecessary.

The safety and efficacy of topical fluoroquinolones for the treatment of ear infections in children and adults is well documented.

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