TEXAS Health and Human Services

Ciprofloxacin and dexamethasone otic suspension

(CIPRODEX®, Alcon Laboratories®)

Classification:

Fluoroquinolone antibiotic and corticosteroid.

Description:

Ciprofloxacin/dexamethasone otic suspension (CIPRODEX®) is a sterile, preserved suspension for otic use supplied as 7.5mL within a single Drop-Tainer® system containing ciprofloxacin and dexamethasone. Each milliliter contains ciprofloxacin hydrochloride 0.3% (equivalent to 3 mg ciprofloxacin base) and dexamethasone 0.1 % (equivalent to 1 mg dexamethasone. Ciprofloxacin/dexamethasone otic suspension also contains the following inactive ingredients: benzalkonium chloride; boric acid; sodium chloride; hydroxyethyl cellulose; tyloxapol; acetic acid; sodium acetate; edetate disodium and water. May contain sodium hydroxide and/or hydrochloric acid to adjust the pH. (1)

Pharmacology:

Ciprofloxacin is a fluoroquinolone antibiotic and is bactericidal against most aerobic and facultative gram-positive and gram-negative organisms. It works by interfering with the enzyme DNA gyrase which is essential for bacterial DNA synthesis. Dexamethasone is a corticosteroid that helps decrease the inflammatory response during bacterial infections. (2)

Pharmacokinetics:

Absorption

- The active components of ciprofloxacin/dexamethasone otic suspension are systemically absorbed following otic administration. With bilateral otic administration of recommended doses, peak plasma concentrations of ciprofloxacin were about 0.1% of those observed after a 250mg oral ciprofloxacin dose. Peak levels of dexamethasone were approximately 14% of those achieved after an oral dexamethasone dose of 0.5mg. (3)

Distribution

- Ciprofloxacin/dexamethasone otic suspension exerts most of its effects locally within the aural canal. However, in pediatric

patients given a bilateral single otic dose post-tympanostomy tube insertion, mean peak plasma levels of ciprofloxacin and dexamethasone were 1.4 ng/mL and 1.1 ng/mL on average respectively. Time to peak levels for each component ranged from 15 minutes to 2 hours. (3)

Metabolism

- Ciprofloxacin undergoes extensive metabolism in the liver. (4) Dexamethasone also utilizes the liver for metabolism but the extent is unknown. (5)

Elimination

- Elimination values for the otic preparation are not available but oral ciprofloxacin is cleared renally and has a half-life of 3-6 hours. (4) Dexamethasone is also renally eliminated and has a half-life of 1.8-2.2 hours. (6)

Indications:

Ciprofloxacin/dexamethasone otic suspension is indicated for the treatment of infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed:

- Acute Otitis Media in pediatric patients (age ≥ 6 months), with tympanostomy tubes, due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* or *Pseudomonas aeruginosa*.
- Acute Otitis Externa in pediatric patients (age ≥ 6 months), adult patients, and elderly patients due to *Staphylococcus aureus* and *Pseudomonas aeruginosa.* (1)

Dosage:

Four drops instilled into the affected ear twice daily for seven days. (1)

Administration:

The suspension should be warmed by holding the bottle in the hand for one or two minutes to avoid dizziness, which may result from the instillation of a cold suspension. The patient should lie with the affected ear upward, and then the drops should be instilled. This position should be maintained for 60 seconds to facilitate penetration of the drops into the ear canal. If the patient has tympanostomy tubes, the tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed. (1)

Contraindications:

This medication is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the

components in this medication. It is also contraindicated in patients with viral infections of the external canal including herpes simplex infections and fungal otic infections. (1)

Warnings and Precautions:

Hypersensitivity Reactions

- Ciprofloxacin/dexamethasone otic suspension should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching.

Microbial Overgrowth

- Prolonged use of ciprofloxacin/dexamethasone otic suspension may result in overgrowth of non-susceptible, bacteria and fungi. If the infection does not improve after one week of treatment, cultures should be obtained to guide further treatment. If such infections occur, discontinue use and institute alternative therapy based on microbial sensitivities.

Continued or Recurrent Otorrhea

- If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor. (1)

Interactions:

The use of ciprofloxacin/dexamethasone otic suspension with agents that can prolong the QTc interval is contraindicated as ciprofloxacin can also prolong the QTc interval. The combined QTc prolongation may not be as clinically relevant with the otic administration versus systemic administration, however dual therapy with agents that prolong the QTc interval should be closely followed. Clinicians should weigh the risks and benefits of starting ciprofloxacin/dexamethasone otic suspension in patients who are already taking an agent that prolongs the QTc interval. (2)

Adverse Reactions:

The common reactions include: Ear discomfort 3%; otalgia 0.4-2.3%; and pruritus of skin 1.5%. The serious adverse reactions include:

Erythematous rash; hypersensitivity reaction; superimposed infection of ear 0.6%; and Otorrhea. (2)

Use in Special Populations:

Pregnancy

- No adequate/well controlled studies have been performed in pregnant women and caution should be exercised when using ciprofloxacin/dexamethasone otic suspension in this population.

Lactation

- It is not known whether topical otic administration of ciprofloxacin or dexamethasone results in sufficient systemic absorption to produce detectable quantities in human milk. Because of the potential for unwanted effects in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Patients

- The safety and efficacy of ciprofloxacin/dexamethasone otic suspension has been established in pediatric patients 6 months and older in adequate and well-controlled clinical trials. (1)

Product identification:

Ciprofloxacin/dexamethasone sterile otic suspension is a white suspension supplied as 7.5 mL in a DROP-TAINER® system. This system consists of a polyethylene bottle and plug, with a white polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package. (1)

Storage:

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). Avoid freezing and protect from light. Discard unused portion after therapy has been completed (after 7 days). (1)

Monitoring:

Clinical improvement should be seen within 1 week of treatment. Further evaluation is warranted if otorrhea persists after 7 days, or 2 or more episodes of otorrhea occurs within 6 months. (3)

Hospital Costs:

Average Wholesale Price $262.33 per 7.5 mL bottle. Bottles cannot be shared between patients, each bottle contains approximately 112 drops. At the recommended dosage, approximately 112 drops are required for full

treatment of both ears. If only treating one ear, or if any portion of the suspension remains after the course of treatment, the unused portion must be discarded. (1)

Efficacy:

While otitis media can be viral in etiology, it is most commonly bacterial and most commonly occurs in children (<2 years old) because the Eustachian tubes are not anatomically developed enough to facilitate proper drainage at this age. (7) The 3 most common bacterial pathogens in otitis media are *Streptococcus pneumoniae*, non-type-able *Haemophilus influenzae*, and *Moraxella catarrhalis*. (8) Nearly all (98%) cases of otitis externa in North America are bacterial. (9) The most common bacterial pathogens in otitis externa are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Other pathogens are principally gram-negative organisms and are responsible for no more than 2-3% of cases. (10) Fungal involvement is uncommon in primary otitis externa but may be more common in chronic otitis externa or after treatment of otitis externa with antibiotics. (11)

Data Sets # 1-3: The following data was provided by the manufacturer and was obtained from multi-center controlled clinical trials comparing topical antibiotic/steroid combinations including ciprofloxacin/dexamethasone otic suspension with neomycin/polymyxin-b/hydrocortisone solution (NEO/POLY/HC). While the studies remain unpublished, the differences in therapy appears clinically significant. (1)

Data Set #	**Clinical Trial**	**Intervention**	**Outcomes**	**Result**
1	Acute Otitis **Media** with Tympanostomy (AOMT) (1)	1. Ciprofloxacin/ dexamethasone otic suspension (BIDx7 days) 2. Ofloxacin 0.3% (BIDx10 days)	1. CC **86%, 90%*** ME **91%**** 2. CC 79%, 79%* ME 82%**	Ciprofloxacin/ dexamethasone otic suspension demonstrated higher clinical cure and microbial eradication rates than ofloxacin in patients with AOMT
2	Acute Otitis **Externa** (AOE) (1)	1. Ciprofloxacin/ dexamethasone otic suspension (BIDx7 days) 2. NEO/POLY/HC (QID)	1. CC **87%, 86%*** ME **86%**** 2. CC 84%, 84%* ME 85%**	Ciprofloxacin/ dexamethasone otic suspension demonstrated higher clinical cure and microbial eradication rates than NEO/POLY/HC in patients with AOE

Data Set #	Clinical Trial	Intervention	Outcomes	Result
3	Acute Otitis **Externa** (AOE) (1)	1. Ciprofloxacin/ dexamethasone otic suspension (BIDx7 days) 2. NEO/POLY/HC (QID)	1. CC **94%, 92%*** ME **92%**** 2. CC 89%, 89%* ME 85%**	Ciprofloxacin/ dexamethasone otic suspension demonstrated higher clinical cure and microbial eradication rates than NEO/POLY/HC in patients with AOE

*Clinical Cure (CC) rates among culture positive patients
**Bacteriologic Cure Rates (Microbial Eradication [ME] rate)

Data Sets # 4-6: The following data sets are a summary of published reviews of relevant RCTs comparing various topical treatments (antimicrobial, steroid, antiseptic, etc.) Details and outcomes are listed below.

Data Set #	**Review**	**Design**	**Outcomes**	**Result**
4	Systematic Review of Topical Antimicrobials for AOE (12)	Eighteen RCTs comparing: 1. Antimicrobial vs placebo 2. Antimicrobial vs antiseptic 3. **Quinolone vs nonquinolone** 4.Steroid/ antimicrobial vs antimicrobial 5.Steroid/ antimicrobial vs steroid	1. Antimicrobial was more effective than placebo: 46%* (95%, CI 29%-63%), 61%** (95%, CI 46-76%) 2. No significant difference 3. **Quinolones were more effective than nonquinolone by +8%* (95%, CI 1%-16%)** 4. No significant difference 5. No significant difference	Topical antimicrobial is effective for AOE with clinical cure rates of 65% to 80% within 10 days of therapy.
5	Cochrane Systematic Review of Interventions for AOE (13)	Nineteen RCTs comparing: 1.Steroid/ antimicrobial vs placebo 2.Steroid/ antimicrobial vs acetic acid	1. Steroid/antimicrobial was more effective than placebo by 11%* (95% CI 2.00 to 60.5) 2. Steroid/antimicrobial was more effective than acetic acid by 29%* (95% CI 0.13 to 0.62) and 25%** (95% CI 0.11 to 0.58)	Topical treatments alone are effective for AOE.

Data Set #	Review	Design	Outcomes	Result
6	Meta-analysis of Steroids and Antimicrobials in AOE (14)	Twelve RCTs comparing: 1. Steroid/ nonquinolone vs quinolone monotherapy	1. Quinolones achieved significantly higher cure rates compared to combination drugs not containing a quinolone. (OR: 1.29; 95% CI: 1.06-1.57; p = 0.01)*, (OR: 1.44; 95% CI: 1.03-2.02; p = 0.03)**	Quinolones have demonstrated a clinical benefit vs steroid/ nonquinolone combination drugs in the treatment of AOE

*Clinical Cure rates
**Bacteriologic Cure Rates

Data Set #7: The following data set compares the efficacy of topical therapy (ciprofloxacin/dexamethasone) with systemic therapy (oral amoxicillin/clavulanate) as reported from a randomized, observer-masked, parallel-group, multicenter trial.

Data Set #	Clinical Trial	Intervention	Outcomes	Results
7	AOMT (15)	1. Ciprofloxacin/ dexamethasone otic suspension (BIDx7 days) 2. Amoxicillin/ Clavulanate. (BIDx10 days)	1. CC 85% Ear pain 5.1% 2. CC 59% Diarrhea 19.5% dermatitis 7.3% stomach pain 4.9%	Topical treatment with Ciprofloxacin/dexamethasone otic suspension is superior to treatment with oral amoxicillin/clavulanic acid and resulted in higher clinical cure rates with fewer adverse effects when used for AOMT

Clinical Cure (CC) rates

Conclusion:

Ciprofloxacin/dexamethasone otic suspension has been shown to be safe and efficacious. Additionally, topical therapy avoids prolonged exposure of bacteria to subtherapeutic concentrations of antibiotic and may be less likely to result in selective pressure for resistant organisms. (16) Another consideration is patient satisfaction which is likely superior with the administration of ciprofloxacin/dexamethasone otic suspension. Compliance to therapy and patient satisfaction are highest when drops are easy to administer, which entails less frequent dosing, shorter duration of therapy, or both. Ciprofloxacin/dexamethasone otic suspension is administered twice daily for only 7 days versus NEO/POLY/HC that is administered four times daily for 10 days. One may consider using ciprofloxacin otic suspension with dexamethasone sodium phosphate ophthalmic solution in the interest of cost reduction. In this case, the increased ease of administration and less volume administered with ciprofloxacin/dexamethasone otic suspension would increase patient compliance and comfort and potentially outweighs the cost reduction benefit of splitting up the medications into two separate administrations.

Recommendation

It is recommended that ciprofloxacin/dexamethasone otic suspension is added to the formulary.

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