Ofloxacin Otic Solution 0.3% (Floxin® [DSC])

Classification

Fluoroquinolone Antibiotic

Pharmacology

Ofloxacin has in vitro activity against a wide range of gram-negative and gram-positive microorganisms. Ofloxacin exerts its bactericidal activity by inhibiting DNA gyrase, an essential enzyme which assists in DNA replication, repair, deactivation and transcription.

An advantage of topical therapy is the high concentration of antibiotic that can be delivered to the site of infection; prolonged exposure to subtherapeutic antibiotic concentrations can lead to the selection of resistant microorganisms.

Indication

Otitis Externa in adults and pediatric patients, 6 months and older, due to *Escherichia coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus.*

Chronic Suppurative Otitis Media in patients 12 years and older with perforated tympanic membranes due to *Proteus mirabilis, Pseudomonas aeruginosa,* and *Staphylococcus aureus*.

Acute Otitis Media in pediatric patients one year and older with tympanostomy tubes due to *Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Streptococcus pneumoniae.*

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	A maximum serum concentration of 10 ng/mL was reported in adults with perforated tympanic membranes. In 2 single-dose (10 drops) studies looking at adults with tympanostomy tubes with and without otorrhea, mean ofloxacin serum concentrations were 4.1 ng/mL and 5.4 ng/mL.
Distribution	After oral administration, ofloxacin has been detected in lung tissue, blister fluid, cervix, ovary, prostatic fluid, prostatic tissue, sputum, and skin.
Metabolism	Minimally metabolized in the liver when ofloxacin is taken orally with doses of 100 to 600 mg.
Excretion	Oral ofloxacin is cleared renally with a half-life of 5-7.5 hours. Approximately 72% - 98.5% of ofloxacin remains unchanged in urine within 48 hours.

Dosage/Administration

Pediatric Dosing

Indication	Dosing
Otitis Externa	From 6 months to 13 years old: 5 drops (0.25 mL/0.75 mg ofloxacin) instilled into the affected ear once daily for 7 days
Acute Otitis Media with tympanostomy tubes	From 1 – 12 years old: 5 drops (0.25 mL/0.75 mg ofloxacin) instilled into the affected ear twice daily for 10 days

Adult Dosing

Indication	Dosing
Otitis Externa	From 13 years and older: Instill 10 drops into affected ear(s) once daily for 7 days; may extend an additional 7 days if symptoms are improving but not yet resolved
Chronic Suppurative Otitis media	Instill 10 drops into affected ear(s) twice daily for 14 days

The bottle should be held in hand for 1-2 minutes to warm up and avoid dizziness from instilling cold solution into ear. Patient should lie down with affected ear pointing upward, then solution drops should be instilled after. Remain in lying down position for five minutes to ensure penetration of the solution into the ear canal.

Use in Special Populations

Pregnancy: Category C. Adverse events have been observed in some animal reproduction studies. There are, however, no adequate and well-controlled studies in pregnant women. Ofloxacin has not been shown to have any adverse effects on the developing embryo or fetus at doses relevant to the amount of ofloxacin that will be delivered ototopically at the recommended clinical doses. Ofloxacin otic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Lactation: Unlike the oral formulation, it is unknown if ofloxacin otic solution is excreted into breast milk. The manufacturer recommends patient-provider decision making to weigh benefits and risk, such as potentially serious adverse events in infants.

Pediatric Use: Safety and efficacy have been demonstrated in pediatric patients of the following ages for the listed indications. Safety and efficacy in pediatric patients below these ages have not been established.

- Six months and older: otitis externa with intact tympanic membranes
- One year and older: acute otitis media with tympanostomy tubes
- Twelve years and older: chronic suppurative otitis media with perforated tympanic membranes

Geriatric Use: No dosage adjustment necessary.

Hepatic Impairment: No dosage adjustment necessary in hepatic impairment.

Renal Impairment: No dosage adjustment necessary in renal impairment.

Contraindication

History of hypersensitivity to ofloxacin, to other quinolones, or to any of the components in this medication.

Precautions

- NOT FOR OPHTHALMIC USE
- NOT FOR INJECTION
- Prolong use of ofloxacin may lead to fungal or bacterial superinfection. Discontinue therapy and switch to alternative if this occurs if there are no improvements after one week. Cultures should be collected to decide next steps. If otorrhea continues after a full treatment course, or if $\geq$2 episodes of otorrhea occur within six months, further evaluation is recommended to exclude other conditions such as cholesteatoma, foreign body, or a tumor.

- The systemic administration of quinolones, including ofloxacin at doses much higher than given or absorbed by the otic route, has led to lesions or erosions of the cartilage in weight-bearing joints and other signs of arthropathy in immature animals of various species. Young growing guinea pigs dosed in the middle ear with 0.3% ofloxacin otic solution showed no systemic effects, lesions or erosions of the cartilage in weight-bearing joints, or other signs of arthropathy. No drug-related structural or functional changes of the cochlea and no lesions in the ossicles were noted in the guinea pig following otic administration of 0.3% ofloxacin for one month.
- Hypersensitivity reactions, such as anaphylactic shock and anaphylaxis, can occur with systemic quinolones. Some were accompanied by airway obstruction, loss of consciousness, or edema. Discontinue treatment if an allergic reaction occurs.

Adverse Effects

Subjects with Otitis Externa

Phase III clinical trials studied once-daily dosing for ofloxacin otic solution in 799 patients with otitis externa and intact tympanic membranes. That studies which are the basis for approval were study 020 (pediatric, adolescents, and adults), 016 (adolescents and adults) and 017 (pediatric). The chart below displays treatment-related adverse events that occurred in two or more patients.

Adverse Events of Subjects with Otitis Externa

Adverse Events	Incidence Rate Studies 002/003 BID (N=229) [a]	Incidence Rate Studies 016/017 QD (N= 310) [a]	Incidence Rate Study 020 QD (N=489) [a]
Application Site Reaction	3%	16.8% [b]	0.6%
Pruritus	4%	1.2%	1.0%
Earache	1%	0.6%	0.8%
Dizziness	1%	0.0%	0.6%
Headache	0%	0.3%	0.2%
Vertigo	1%	0.0%	0.0%

[a] Studies 002/003 (BID) and 016/017 (QD) were active-controlled and comparative. Study 020 (QD) was open and non-comparative.

[b] The increased incidence might be the result of specific questioning towards the patients, since both drug and active control displayed similar incidence rates.

Subjects with Acute Otitis Media with Tympanostomy Tubes (AOM TT) & Subjects with Chronic Suppurative Otitis Media (CSOM) with Perforated Tympanic Membranes

In phase III clinical trials, the treatment-related adverse events listed below occurred in >1% in the 656 patients with non-intact tympanic membranes in AOM TT or CSOM with twice daily dosing of ofloxacin otic solution.

Adverse Events	Incidence (N=656)
Taste Perversion	7%
Earache	1%
Pruritus	1%
Paresthesia	1%
Rash	1%
Dizziness	1%

Cases of uncommon transient neuropsychiatric disturbances have been included in spontaneous post-marketing reports. A causal relationship with ofloxacin otic solution 0.3% is unknown.

Monitoring

- Toxicity: Signs and symptoms of ofloxacin toxicity, such as hot and cold flushes, drowsiness, nausea, and slurring of speech
- Efficacy: Sign and Symptom of improvement

Interactions

Specific drug interactions have not been studied with ofloxacin otic solution. There are also no known significant interactions.

Efficacy

Jones and colleagues

In a randomized, evaluator-blind, multi-center trial, the safety and efficacy of ofloxacin otic solution (0.3%) was compared to that of Cortisporin otic solution

(neomycin sulfate, polymyxin B sulfate, and hydrocortisone) in adults (n = 247) and children (n = 227) with otitis externa (OE). Inclusion criteria included clinically diagnosed, unilateral or bilateral OE of $\leq$ two weeks' duration with purulent or mucopurulent otorrhea. Patients with perforated tympanic membranes within previous six months were excluded. If randomized to ofloxacin 0.3%, adults and children received 0.5 ml (10 drops) and 0.25 ml (5 drops), respectively, twice daily for 10 days. If randomized to Cortisporin otic solution, adults and children received 0.2 ml (4 drops) and 0.15 ml (3 drops), respectively, four times daily for 10 days.

The overall response was cure in 97% of ofloxacin-treated children vs 95% of Cortisporin-treated children (p = 0.48) and 82% of ofloxacin-treated adults vs 84% of Cortisporin-treated adults (p = 0.56). There were no statistically significant differences in microbiological cure or AE's between the two treatment groups.

Torun and colleagues

In a multicenter, open-label, Phase III study, Torun and colleagues evaluated efficacy and safety profile of seven days of once-daily ofloxacin otic 0.3% solution in the treatment of otitis externa. Inclusion criteria included age $\geq$ 6 months, symptom duration of < two weeks, moderate to severe edema and tenderness involving 1 or both ears, an intact tympanic membrane, and sufficient exudate for microbiologic culture. Children aged 6 months to < 13 years received 5 drops once daily for 7 days; adolescents and adults received 10 drops once daily for 7 days.

Study subjects were examined at baseline, end of therapy (EOT, day 7), and test-of-cure (TOC, day 14-17). The primary efficacy end point was success (complete resolution of all signs and symptoms) or failure (all other responses). A culture was taken at baseline and if secretion was still present at the EOT visit, another specimen was collected for microbiologic analysis. Compliance/adherence was assessed at the EOT visit (patient diary). Researchers evaluated patients (n = 439) who did not use prohibited treatment and received $\geq$ 6 doses of ofloxacin otic solution and returned for the EOT and TOC visits. Also included were patients whose symptoms did not improve after $\geq$ 3 days of treatment with the study drug (clinical failures).

The clinical cure rate was 91%--68% of patients were cured by the EOT visit, 23% were cured within 7 to 10 days thereafter (TOC visit). Fifty-eight (58%) of patients were microbiologically evaluable (n = 253) and the microbiologic eradication rate was 96%. *P aeruginosa* was isolated from 158 (62%) patients and was eradicated in 153 (97%) of them; of patients infected with *P aeruginosa*, 143 (91%) were clinically cured. *S aureus* was isolated from 32 (13%) patients and eradicated in 31

(97%) of them; 24 (75%) patients infected with *S aureus* were cured. 98% of patients were compliant.

The authors concluded that the efficacy and safety profile of ofloxacin otic 0.3% solution were not compromised by being administered once daily for 7 days rather than twice daily for 10 days as in earlier OE trials. This reduced treatment course may contribute to increased patient adherence and greater rates of treatment completion.

Name	Dosing Frequency	Form	Price (GoodRx)
Ofloxacin 0.3%	Once daily	Otic solution	$42.54, 5 ml
Ciprofloxacin-dexamethasone (Ciprodex)	BID	Otic suspension	$75.95, 7.5 ml
Ciprofloxacin-hydrocortisone (non-sterile)	BID	Otic suspension	$336.29, 10 ml
Ciprofloxacin 0.2%	BID	Otic solution	$55.71 per carton (14 containers)

Safety Considerations

- Look Alike-Sound Alike: Floxin may be confused with Flexeril. Floxin is currently discontinued in the United States, but generic is available.

Summary/Conclusion

In a strong recommendation, Rosenfeld RM et al (2014) state that clinicians should not prescribe systemic antimicrobials as initial therapy for diffuse, uncomplicated AOE unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy. FDA approved topical agents for the treatment of AOE include the following: acetic acid solution (q 4-6 h); acetic acid/hydrocortisone (q 4-6 h); ciprofloxacin/hydrocortisone (non-sterile, BID); ciprofloxacin/dexamethasone (BID); neomycin, polymyxin B, hydrocortisone (TID-QID); ofloxacin 0.3% (once daily) and ciprofloxacin 6%.

According to Rosenfeld RM et al (2014), there are no meaningful differences in clinical outcomes based on class of therapy (antibiotic vs antiseptic), use of a quinolone versus a non-quinolone, or monotherapy versus combination drugs with or without a concurrent steroid. For the treatment of otitis externa, Sanford (2023) recommends the following: (1) ciprofloxacin + (dexamethasone or hydrocortisone) bid x 7 days; (2) ofloxacin qd x 7 days; (3) ciprofloxacin single dose. Ciprofloxacin plus hydrocortisone is a non-sterile formulation and needs to be avoided in patients

who do not have an intact ear drum because of increased infection risk. Compared to ciprofloxacin + dexamethasone, ofloxacin is less expensive and has the advantage of once-daily dosing.

Recommendation

Ofloxacin 0.3% otic should be added to the formulary.

References

1. Rosenfeld RM, Schwartz SR, Cannon CR, et al. Clinical Practice Guideline: Acute Otitis Externa. Otolaryngology—Head and Neck Surgery 2014, Vol 150(IS) S1-S24
2. Gilbert DN, Chambers HF, Saag MS, et al. The Sanford Guide to Antimicrobial Therapy 2023. 53th edition.
3. Clinical Resource, Prevention and Treatment of Swimmer's Ear. Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber's Letter. June 2023.
4. Torum B, Block SL, Avila H, et al. Efficacy of Ofloxacin Otic Solution Once Daily for 7 Days in the Treatment of Otitis Externa: A Multicenter, Open-Label, Phase III Trial. Clin Ther 2004;26:1046-54.
5. Jones RN, Milazzo J, Seidlin M. Ofloxacin Otic Solution for Treatment of Otitis Externa in Children and Adults. Arch Otolaryngol Head Neck Surg. 1997;123:1193-1200.
6. Ofloxacin Otic solution 0.3% prescribing information. Apotex Corp. Revised 11/2022.

Date: January 12, 2024
Prepared by: Nathalie Nguyen, University of Texas College of Pharmacy P4 student
Reviewed by: Catherine Hall, PharmD, BCPP, BCACP