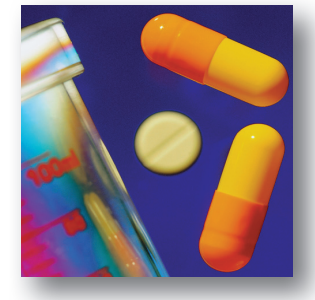

Otiprio: An FDA-Approved Ciprofloxacin Suspension Gel for Pediatric Otitis Media With Effusion

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INTRODUCTION

Otitis media (OM), inflammation of the middle ear, is the most common condition for which antibiotics are prescribed for children in the United States.[1] Treatment of acute OM focuses on eradication of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, the bacteria types most frequently associated with these infections.[2] Children may also develop persistent fluid in the middle ear, also known as otitis media with effusion (OME), in the presence of or in the absence of an acute ear infection. Some may continue to suffer from recurrent episodes of acute OM and are often referred to otolaryngologists for consideration of tympanostomy tube (TT) placement. TT placement (TTP) in children with recurrent acute OM or chronic OME is the most common pediatric ambulatory surgery in the United States,[3] with approximately one million surgeries being performed annually.[4]

The most common complication of TTP is postsurgical otorrhea (discharge from the ear), which may occur in as many as 50% of patients within the first two weeks following surgery and in more than 80% of patients within 18 months of surgery.[5,6] Otolaryngologists routinely administer topical antibiotic drops at the time of surgery, and for a short duration following surgery, the drops are administered at home by a caregiver to try to reduce the rate of postoperative otorrhea.

The clinical practice guideline published in 2013 strongly recommends topical antibiotic therapy instead of oral antibiotic therapy in the treatment of acute post-TTP otorrhea.[7] Comparisons of topical antibiotic eardrops (ofloxacin, ciprofloxacin, or ciprofloxacin-dexamethasone) to systemic oral antibiotics (amoxicillin or amoxicillin-clavulanate) have been conducted in randomized clinical trials in children treated for post-TTP otorrhea.[8–10] Topical therapy showed superiority in clinical cure,[8–10] bacterial eradication,[9] and patient satisfaction.[9] Topical therapies are delivered directly, bypassing intestinal absorption and hepatic first-pass effects that can affect tissue concentrations and potentially reducing systemic adverse effects compared with oral administration.[8] For example, topical ciprofloxacin has shown 1,000-fold higher tissue concentrations compared with oral administration.[11]

Although not approved by the Food and Drug Administration (FDA) for this indication, topical antibiotic regimens are used by otolaryngologists at the time of TTP because they are relatively effective; however, these regimens may still present treatment challenges. Postoperatively, parents may be hesitant to place the drops consistently if the child becomes fussy at the time of administration or if the child complains the drops are "hurting their ears." In addition, at the time of the procedure, the surgeon can visualize and maximize the amount of drops entering the middle ear via the tube lumen, but caregivers have no way of determining if the drops have reached the tube.[12] Lastly, because antibiotic drops usually require multiple drops given twice daily administered over multiple days, caregiver compliance is a concern, with failure to adhere to the regimen possibly promoting the selection of resistant pathogens.

As a result of these challenges, there had been a need for an FDA-approved, single-dose antibiotic therapy that could be administered by the otolaryngologist at the time of TTP. This would eliminate compliance issues by the caregiver, ensure reliable drug delivery to the middle ear, provide a sustained delivery of antibiotic in the middle ear, and address pharmacokinetic limitations associated with aqueous drops that are rapidly eliminated from the middle ear compartment.

A topical treatment, ciprofloxacin otic suspension 6% (Otiprio, Otonomy, Inc.), was developed to address these issues and received FDA approval in December 2015.[13] Ciprofloxacin has been shown to be active against most isolates of gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus pneumoniae*) and gram-negative bacteria (*H. influenzae*, *M. catarrhalis,* and *Pseudomonas aeruginosa*).[13] This *Drug Forecast* will discuss this single-dose, physician-administered treatment that combines a thermosensitive gel with ciprofloxacin microparticles. It is the first FDA-approved treatment for pediatric patients with bilateral OME undergoing TTP. Preclinical and clinical trial results are described as well as treatment, preparation, administration, and considerations for use.

OVERVIEW

A suspension of ciprofloxacin in poloxamer 407 (initially known as OTO-201 and now branded as Otiprio) was developed and exhibited sustained exposure pharmacokinetics. At the concentration studied, the poloxamer vehicle exhibited thermoreversible properties. Otiprio is in liquid form at or below room temperature, but quickly transitions to a gel at body temperature once it is administered. As a result, exposure of the middle ear

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to ciprofloxacin was shown to be as long as 10–14 days following a single administration in animal studies.[14]

PRECLINICAL STUDIES

Preclinical studies evaluating a single administration of OTO-201 were conducted in guinea pigs and chinchillas to characterize the pharmacokinetic profile and toxicological potential of OTO-201 in both the middle ear and inner ear.[14] The study conducted in guinea pigs compared a single intratympanic injection of OTO-201 (administered at various doses) in the middle ear anterior to the round window membrane with a twice-daily, seven-day regimen of ciprofloxacin/dexamethasone otic suspension (Ciprodex, Alcon) or ciprofloxacin otic solution 0.2% (Cetraxal, WraSer Pharmaceuticals). A single intratympanic dose of OTO-201 provided high peak drug concentrations (C_{max}) and a steady dose of ciprofloxacin, with progressive decline over time. Disappearance from the middle ear was strongly dependent on the dose of OTO-201. A single application of ciprofloxacin/dexamethasone otic suspension drops resulted in a contrasting profile: ciprofloxacin C_{max} was much smaller and declined sharply within hours of administration. The pulsatile regimen of ciprofloxacin/dexamethasone otic suspension administration was evidenced by a rapid cycling of free ciprofloxacin levels in the middle ear. Similar findings were seen with ciprofloxacin otic solution 0.2% administration. The higher C_{max} values seen with OTO-201 resulted in a higher degree of drug exposure, as evidenced by the higher area under the curve levels.

Using a chinchilla model, the ability of OTO-201, ciprofloxacin/dexamethasone otic suspension, and ciprofloxacin otic solution 0.2% to eliminate *Streptococcus pneumoniae*-induced OM was investigated. Both the ciprofloxacin/dexamethasone otic suspension and ciprofloxacin otic solution 0.2% reduced the load of bacteria in the middle ear (greater than 5–6 log orders) and the extent of middle ear effusion. With the first dose of ciprofloxacin/dexamethasone otic suspension, the bacterial titer dropped by approximately 4 logs within the first six hours, but evidence of bacterial regrowth was seen between applications. Time to clinical cure was measured at 72 hours. All doses of OTO-201 reduced the middle ear bacterial load (6–8 log orders) and middle ear effusion to levels that were seen with ciprofloxacin/dexamethasone otic suspension and ciprofloxacin otic solution 0.2%, with the exception of the lowest OTO-201 dose tested. A single dose of OTO-201 resulted in clinical cure within 18 hours of treatment.

A toxicological evaluation was performed one month after a recovery period in the same study. Treatment with the ciprofloxacin/dexamethasone otic suspension and ciprofloxacin otic solution 0.2%, which were administered twice daily for seven days, resulted in a mild-to-moderate hair cell loss, confined to the apical half of the cochlea, possibly indicative of mild ototoxicity. In contrast, OTO-201 given at doses up to 6% did not induce hair cell loss or apparent cochlear pathology. None of the tested products produced evidence of tube occlusion.

CLINICAL STUDIES

Phase 1b Trial

As noted earlier, topical therapies are delivered directly to the desired area and may therefore reduce systemic adverse effects compared with oral administration.[8] In the case of OTO-201, a waiver of *in vivo* bioavailability in humans was granted by the FDA during the approval process. OTO-201 is expected to have negligible systemic exposure, and challenges exist in measuring middle ear pharmacokinetic concentrations in humans. As such, no clinical pharmacokinetic studies were conducted with OTO-201.[13]

A double-blind, randomized, prospective, placebo- and sham-controlled, multicenter phase 1b trial was conducted in children 6 months to 12 years of age with bilateral middle ear effusions requiring TTP.[15] The objective of the study was to evaluate the safety and clinical activity of OTO-201 administered during TTP in children. Patients were randomized to intraoperative OTO-201 (4 mg or 12 mg) with TTP, placebo with TTP, or TTP alone (2:1:1 ratio).

Eighty-three patients were followed for safety (with otoscopic exams, cultures, audiometry, and tympanometry) and clinical activity, which was defined as treatment failure (physician-observed otorrhea and/or the need for a systemic antibiotic three or more days postoperatively). At each visit, the proportion of treatment failures was lower in both OTO-201 dose groups when compared with the pooled placebo and TTP alone group. When observed through day 15, 14.3%, 15.8%, 45.5%, and 42.9% of patients who received OTO-201 4 mg, OTO-201 12 mg, placebo, and TTP alone, respectively, were defined as treatment failures. The reduction of treatment failures for the two OTO-201 groups, compared with placebo and TTP alone, was seen as early as the first postoperative visit on day 4.

There were no serious adverse events related to the trial drug, and no adverse events led to discontinuation of patients from the trial. Even though the sample size was small, use of OTO-201 was not associated with loss of tube patency or early tube displacement. Baseline audiometric assessment showed that most patients had an air–bone gap (greater than 10 decibels [dB]) across the frequencies from 500 to 2,000 Hz. Audiometric reassessment at the end of the trial showed the proportion of patients with an air–bone gap greater than 10 dB was reduced to approximately 30% or less for each treatment group and frequency. Tympanogram types on day 15 revealed that the majority of patients (approximately 80%) progressed to a type B tympanogram (large volume), indicating tube patency and a normal middle ear. The results from this phase 1b trial led to the initiation of subsequent phase 3 clinical trials.

Phase 3 Trials

Two identical phase 3 clinical trials, which enrolled 532 pediatric patients at 53 centers in the United States and Canada, were conducted to investigate the safety and efficacy of a single intraoperative administration of 0.1 mL OTO-201 (6 mg) in children requiring TTP.[13,16,17] Patients 6 months to 17 years of age were eligible for the study if they had effusions in both ears at the time of TTP. Patients were randomized into groups to receive TTP with OTO-201 or TTP alone. Treatment with OTO-201 was administered by the surgeon in the operating room following myringotomy and suctioning of the middle ear effusion and prior to placement of the tube. Follow-up visits occurred on days 4, 8, 15, and 29 after surgery. An analysis of baseline demographics is shown in Table 1.

Table 1 Baseline Demographics of OTO-201 Phase 3 Clinical Trials[16]*

Characteristic	Trial 1 (N = 266)		Trial 2 (N = 266)	
	OTO201 With TTP (n = 179)	TTP Alone (n = 87)	OTO201 With TTP (n = 178)	TTP Alone (n = 88)
Age in years, mean (SD)	2.4 (2.1)	2.5 (2.1)	2.3 (1.9)	2.9 (2.6)
Gender, no. (%)				
Male	104 (58.1)	56 (64.4)	96 (53.9)	48 (54.5)
Female	75 (41.9)	31 (35.6)	82 (46.1)	40 (45.5)
Ethnicity, no. (%)				
Hispanic or Latino	24 (13.4)	11 (2.6)	16 (9.0)	10 (11.4)
Non-Hispanic or non-Latino	149 (83.2)	70 (80.5)	162 (91.0)	75 (85.2)
Not reported	2 (1.1)	3 (3.4)	0	1 (1.1)
Unknown	4 (2.2)	3 (3.4)	0	2 (2.3)
Race, no. (%)				
White	148 (82.7)	69 (79.3)	140 (78.7)	72 (81.8)
Black	20 (11.2)	13 (14.9)	23 (12.9)	10 (11.4)
Asian	2 (1.1)	0	2 (1.1)	2 (2.3)
Native American or Canadian	1 (0.6)	0	1 (0.6)	1 (1.1)
Native Hawaiian or other Pacific Islander	0	0	2 (1.1)	0
Not applicable	1 (0.6)	1 (1.1)	1 (0.6)	2 (2.3)
Other	7 (3.9)	4 (4.6)	9 (5.1)	1 (1.1)
Effusion type (≥ one ear), no. (%)				
No type recorded	2 (1.1)	1 (1.1)	3 (1.7)	0
Mucoid	86 (48.0)	36 (41.4)	116 (65.2)	67 (76.1)
Purulent	27 (15.1)	11 (12.6)	22 (12.4)	10 (11.4)
Sanguineous	1 (0.6)	3 (3.4)	0	1 (1.1)
Serous	88 (49.2)	44 (50.6)	57 (32.0)	23 (26.1)
Positive microbiology culture[a]				
≥ One ear	41 (22.9)	22 (25.3)	29 (16.3)	27 (30.7)
One ear	24 (13.4)	11 (12.6)	22 (12.4)	21 (23.9)
Both ears	17 (9.5)	11 (12.6)	7 (3.9)	6 (6.8)

OTO-201 = Otiprio (ciprofloxacin otic suspension 6%); SD = standard deviation; TTP = tympanostomy tube placement.

* Percentages have been rounded and may not total 100.

[a] Indicates baseline (the last measurement obtained on or before the day of randomization) microbiologic culture was positive for at least one of the following: *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

Treatment failure through day 15, the primary endpoint of the phase 3 clinical trials, was defined as the following, whichever occurred first: otorrhea observed by a blinded assessor from day 4 through day 15; use of otic or systemic antibiotics from day 1 through day 15; lost to follow-up; or missed visit. In both studies, significantly fewer treatment failures were observed in the OTO-201 group when compared with tube placement alone (25% versus 45%, $P < 0.001$ in Study 1; and 21% versus 45%, $P < 0.001$ in Study 2). Further analysis was performed to show the specific reason for treatment failure in each trial (Table 2).[16] When considering treatment failures due to observation of otorrhea by the blinded observer, the data showed that OTO-201 reduced the rate of postoperative otorrhea in both trials by 64% at day 15 when compared with TTP alone. Significant decreases in otorrhea were also observed at day 4 and day 8.

In these trials, there were no serious adverse events related to OTO-201, and no patients dropped out of the studies due to an adverse event. In patients randomized to OTO-201 treatment, there was no negative impact on hearing, tympanometry, or otoscopy, and there was no increase in the incidence of tube occlusion.

These two identically designed phase 3 clinical trials concluded that a single intratympanic administration of OTO-201 is a safe and effective new treatment for middle ear effusion at the time of TTP.

SAFETY CONSIDERATIONS

Otiprio is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, other quinolones, or any of the product's components. In the two phase 3 clinical trials, the treatment-emergent adverse events for the OTO-201 treatment group and the TTP-only group were similar and included pyrexia, procedural (postoperative) pain, cough, and upper respiratory tract infection. Adverse events that occurred in at least 3% of OTO-201 patients and at an incidence greater than those who underwent TTP alone included nasopharyngitis (5.0% versus 3.5%), irritability (4.8% versus 2.9%), and rhinorrhea (3.4% versus 1.7%).[17]

PREPARATION

Otiprio is supplied as a preservative-free, white, sterile otic suspension of 6% ciprofloxacin (60 mg/mL) in a neutral pH, buffered isotonic solution in a single-patient-use 1-mL glass vial. The drug should be stored in the original carton, protected from light, and at 36°–46° F (2°–8° C) prior to use to prevent thickening during preparation. It is important to keep the product cold, and placing the vial on an ice pack during preparation may be considered. If Otiprio starts to thicken while being prepared, place the vial back in the refrigerator. The vial should be shaken for five to eight seconds to mix well until a homogenous suspension is obtained. When handling, always hold the vial by the aluminum collar to prevent gelation.

Table 2 Cumulative Proportion of Treatment Failures Through Day 15 in Phase 3 Trials[15]

	Trial 1 (N = 266)		Trial 2 (N = 266)	
	OTO-201 With TTP (n = 179)	TTP Alone (n = 87)	OTO-201 With TTP (n = 178)	TTP Alone (n = 88)
Treatment failure[a]	24.6% (44 of 179)	44.8% (39 of 87)	21.3% (38 of 178)	45.5% (40 of 88)
Reason for failure[b]				
Otorrhea[c]	7.3% (13 of 179)	11.5% (10 of 87)	6.7% (12 of 178)	27.3% (24 of 88)
Otic or systemic antibacterial drugs	7.3% (13 of 179)	21.8% (19 of 87)	8.4% (15 of 178)	11.4% (10 of 88)
Lost to follow-up	0.6% (1 of 179)	0	0.6% (1 of 178)	0
Missed visit	9.5% (17 of 179)	11.5% (10 of 87)	5.6% (10 of 178)	6.8% (6 of 88)

CI = confidence interval; CMH = Cochran–Mantel–Haenszel; OTO-201 = Otiprio (ciprofloxacin otic suspension 6%); TTP = tympanostomy tube placement.

[a] Odds ratios for OTO-201 versus TTP alone for the primary endpoint were 0.39 (95% CI, 0.22–0.68) and 0.30 (95% CI, 0.17–0.53) for Study 1 and Study 2, respectively; $P < 0.001$ for CMH test (adjusted for age group).

[b] The earliest occurring treatment failure event; patients were classified as a treatment failure due to that component only for the remainder of the study.

[c] Odds ratios for otorrhea treatment failures for OTO-201 versus TTP alone were 0.38 (95% CI, 0.19–0.75; $P = 0.004$ for CMH test adjusted for age group) and 0.19 (95% CI, 0.09–0.38; $P < 0.001$ for CMH test adjusted for age group) for Study 1 and Study 2, respectively.

Two types of needles are necessary during preparation. Once the 18–21-gauge (G) needle has been used to draw the suspension into the syringe, the needle should be replaced with a 20–24-G blunt, flexible needle for drug administration. Using the same vial, a second separate syringe should be prepared for the patient's second ear. After preparation, syringes can be kept at room temperature or in the refrigerator prior to administration. Syringes should be kept on their side until used. The syringe should be discarded if it is not used within three hours of preparation.

ADMINISTRATION

From a surgeon's standpoint, the administration of Otiprio in the operating room is simple. The drug is prepared into two separate Luer-lock syringes, one for each ear. A blunt, flexible (20–24-G) needle is attached to each syringe.

After the fluid is suctioned from the patient's middle ear, the flexible needle can be manipulated to guide the tip through the myringotomy incision. By bending the needle, it is easy to approximate the angle provided with an angled myringotomy blade. (This is very helpful if you are a left-handed surgeon.) When the drug is injected into the middle ear, the otic suspension can be observed filling the middle ear space; it is visible as a white suspension behind the tympanic membrane. Upon insertion of the TT through the myringotomy, Otiprio is clearly visible through the tube lumen. Any excess drug can be suctioned from the area, and one can easily visualize the drug changing from a liquid to the gel form in response to body temperature. Although the product gels, suctioning it from any areas outside the middle ear is still possible. Based upon the phase 1b and phase 3 studies showing no evidence of tube occlusion when compared with TTP alone, it does not seem necessary to suction the drug from the tube lumen. At phase 1b and phase 3 trial follow-up visits, ciprofloxacin particles were visible in the middle ear for up to two weeks on otoscopic exam.

Because of the inflammation present at the time of tube placement, it is not unusual for patients to experience some bleeding at the time of myringotomy incision and suctioning of fluid from the middle ear. However, once Otiprio was administered in the clinical trials through the myringotomy incision, there was no noticeable blood draining through or around the tube. Moreover, there were no calls or reports from nurses in the post-anesthesia care unit reporting bloody discharge from the ear canal. At the time of follow-up in the office, there was no observation of bloody crusting in the lumen of the TTs. Based on these observations, it may appear that there is a potential tamponade effect of the poloxamer in Otiprio on the middle ear mucosa.

Another delivery option for administration of Otiprio is application through the tube lumen at the time of surgical placement. An open-label, multicenter phase 3b clinical trial was conducted to evaluate feasibility (volume delivered, ease of administration), efficacy (presence of otorrhea), and safety (otoscopy, adverse events) of this technique.[18] The study included children 6 months to 17 years of age with confirmed bilateral effusions on the day of TTP. A single dose of 0.1 mL containing 6 mg of ciprofloxacin was administered through the tube intraoperatively, and patients returned for observation on days 15 and 29. Otorrhea was observed in 3% of patients at day 15. Feasibility was demonstrated in all patients administered Otiprio through tympanostomy tubes. The investigators noted that, in the younger age stratum of 6 months to 2 years, delivery of the entire 0.1-mL dose was challenging in approximately 50% of ears due to their limited middle ear space. There were no safety issues observed in otoscopic exams and no difference in tube occlusion, findings that were consistent with the phase 3 trials. The results seen in the phase 3 and 3b trials support the flexibility of administering Otiprio before or after tube placement in children with middle ear effusions.

CONCLUSION

Otorrhea or OME may occur in as many as 50% of patients within the first two weeks following TTP.[5,6] Prior to the approval of Otiprio, no FDA-approved agent was indicated to treat pediatric patients with bilateral OME at the time of TTP. A single intratympanic injection of Otiprio at the time of TTP has been shown to provide a sustained release

of ciprofloxacin to the middle ear for as long as two weeks. Single-dose therapy given at the time of TTP eliminates the need for repeat otic drop administration by the caregiver and assures compliance with therapy, ensuring sufficient drug exposure to the middle ear.

Two phase 3 clinical trials[17,18] demonstrated that a single 0.1-mL dose of Otiprio (6 mg), a thermosensitive otic suspension of ciprofloxacin, is a safe and effective treatment for middle ear effusion at the time of TTP. These trials also showed statistically significant lower rates of treatment failure at day 15 compared with TTP alone, less otorrhea, and less use of antibacterial drugs postoperatively. Administration of Otiprio did not result in serious adverse effects compared with TTP alone, impairment of hearing or middle ear function, or any deleterious effect on tube patency versus tubes alone.[17,18]

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