Safety of Besifloxacin Ophthalmic Suspension 0.6% in Cataract and LASIK Surgery Patients

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Purpose: The aim of the study was to evaluate the safety of besifloxacin ophthalmic suspension 0.6% as antibacterial prophylaxis in the surgical setting.

Methods: Two prospective safety surveillance studies were conducted—one in the cataract surgery setting and the other in the laser-assisted in situ keratomileusis (LASIK) surgery setting. Cases from patients aged 18 years and above were eligible for inclusion. In both surveillance studies, data were collected from consecutive cases of routine primary cataract surgery and LASIK surgery, respectively, in which besifloxacin ophthalmic suspension 0.6% or moxifloxacin ophthalmic solution 0.5% was used as the topical perioperative prophylactic antibacterial medication as part of the clinician’s routine standard of care. The primary safety endpoint was the incidence of treatment-emergent adverse events (TEAEs).

Results: The cataract surgery surveillance study included 485 cases/eyes (besifloxacin, n = 333; moxifloxacin, n = 152), whereas the LASIK surveillance study included 456 cases/eyes (besifloxacin, n = 344; moxifloxacin, n = 112). In the cataract study, only 1 TEAE was reported in a besifloxacin case (mild hypersensitivity/allergic reaction considered possibly related to besifloxacin). No TEAEs were reported in the LASIK study. In both studies, surgical outcomes were similar with both treatments. The frequency of preoperative and/or postoperative dosing was generally lower for besifloxacin than that for moxifloxacin.

Conclusions: In prospective safety surveillance studies of patients undergoing cataract extraction or LASIK, TEAEs associated with prophylactic use of besifloxacin ophthalmic suspension 0.6% were rare, and surgical outcomes with besifloxacin were similar to those with moxifloxacin ophthalmic solution 0.5%.

Key Words: adverse drug reactions, besifloxacin, cataract extraction, keratomileusis, laser in situ, moxifloxacin

Cataracts are the leading cause of visual impairment and are primarily managed surgically.1 Cataract extraction is among the most common surgical interventions performed in the United States. The preferred method of cataract removal is extracapsular extraction, most commonly achieved by phacoemulsification (phaco) through small self-sealing corneal incisions. Laser-assisted in situ keratomileusis (LASIK) is the most commonly performed keratorefractive surgery in the United States.2 The procedure involves creating a corneal flap using a mechanical microkeratome or a femtosecond laser, reshaping the exposed corneal stroma using a tissue-ablating excimer laser, and repositioning the flap.

Prevention of infection is important in both cataract and LASIK surgeries, and prophylactic use of topical antibacterials is recommended in both procedures.1,2 Besifloxacin is a chlorofluoroquinolone with a broad-spectrum bactericidal activity against aerobic and anaerobic bacteria.3–6 Besifloxacin ophthalmic suspension 0.6% (Besivance; Bausch & Lomb, Tampa, FL) incorporates a polycarboaryl-based mucoadhesive polymer (DuraSite; InSite Vision, Alameda, CA) that prolongs the drug residence time on the ocular surface and improves bioavailability.6–9 Besifloxacin ophthalmic suspension is indicated for the treatment of bacterial conjunctivitis,10 but as with other topical antibacterial products, it is often used off-label for antibacterial prophylaxis in the surgical setting.

Two prospective surveillance studies were conducted to evaluate the safety of besifloxacin ophthalmic suspension 0.6% when used as a prophylactic antibacterial agent by patients undergoing cataract or LASIK surgery, respectively. For comparative purposes, moxifloxacin ophthalmic solution 0.5% (Vigamox; Alcon Laboratories, Inc, Fort Worth, TX) was also evaluated. Moxifloxacin is an 8-methoxy fluoroquinolone antibiotic that has been used extensively for prophylaxis in the surgical setting with a history of good tolerability.11–13 It has once been described as the preferred treatment for surgical prophylaxis by many.14

MATERIALS AND METHODS

Study Design
The cataract and LASIK surveillance studies were conducted at 10 and 7 sites, respectively, in the United States.
Cases from patients aged 18 years and above were eligible for inclusion. For the cataract and LASIK studies, data were collected on consecutive cases of routine primary cataract surgery (phaco with posterior chamber intraocular lens implantation, not combined with any other surgery) and LASIK, respectively, in which besifloxacin ophthalmic suspension 0.6% or moxifloxacin ophthalmic solution 0.5% was used as the topical perioperative prophylactic antibacterial medication as part of the clinician’s routine standard of care. Each study planned to enroll 500 cases (350 besifloxacin and 150 moxifloxacin).

Each site obtained approval for participation in the surveillance, approval of the protocol, and approval of the informed consent form (and any amendments) from the institution’s institutional review board/ethics committee or the reviewing central institutional review board/ethics committee before entering any patients in the surveillance. Informed consent and Health Insurance Portability and Accountability Act authorization were obtained before the collection of data.

Data collected through electronic data collection forms included demographics; surgical details (date, incision size, and technical information); relevant comorbid conditions; topical ophthalmic medications used preoperatively, on the day of the surgery, and postoperatively; surgical outcomes (final visual acuity and any abnormal ocular findings after the surgery); and treatment-emergent adverse events (TEAEs). The timing for any assessment of surgical outcomes was according to the clinician’s usual practice; the final visual acuity was recorded at the visit when the investigator considered the potential for an impact on safety by the antibacterial agent to no longer exist.

**Statistical Analysis**

The primary safety endpoint was the incidence of TEAEs. A sample size of 350 besifloxacin cases was estimated to provide a 95% confidence of detecting adverse drug reactions with a true frequency of at least 0.9%.

All summaries were done at the eye level; 2 eyes from the same subject were treated as 2 separate records. For continuous variables, the sample size, mean, SD, median, minimum, and maximum were determined. For discrete variables, frequencies and percentages were determined. The Fisher exact test was used to compare the incidence of TEAEs among patients using besifloxacin ophthalmic suspension 0.6% with the comparator. Other between-treatment comparisons were performed with the Cochran–Mantel–Haenszel adjustment for site when appropriate. All statistical tests used a 2-sided α level of 0.05.

**RESULTS**

**Cataract Study**

The study included 485 cases/eyes (besifloxacin, n = 333; moxifloxacin, n = 152). Six of 10 centers provided both besifloxacin and moxifloxacin cases/eyes, 3 provided besifloxacin cases/eyes only, and 1 provided moxifloxacin cases/eyes only. Demographics were similar across the treatment groups (Table 1). The mean age at the time of the surgery was 68.2 years and most patients (56.7%) were female. Comorbid conditions (eg, diabetes mellitus, glaucoma, and smoker) were comparable between treatment groups. Patients commonly used concomitant topical corticosteroids (99.8%) and nonsteroidal antiinflammatory drugs (79.6%); the use of artificial tears was less common (4.7%). Sutureless surgeries were performed in the majority of besifloxacin (89.8%) and moxifloxacin (80.3%) cases, and the mean incision size was 2.3 mm in both the groups. No phaco energy was needed for 10.5% of besifloxacin cases and 28.3% of moxifloxacin cases. When phaco energy was used, besifloxacin cases had a longer mean phaco time (2.5 vs. 0.8 minutes) and a lower mean phaco power (39.2% vs. 46.4%) than those of moxifloxacin cases.

Table 2 presents the frequency and the duration of topical antibacterial use. All besifloxacin cases used the antibacterial agent preoperatively, whereas 15.8% of moxifloxacin cases did not. The frequency of preoperative and postoperative dosing was generally lower for besifloxacin than for moxifloxacin. The most common preoperative and postoperative doses were 3 times daily for besifloxacin and 4 times daily for moxifloxacin. The mean duration of antibacterial use was 14.7 days for besifloxacin cases and 12.0 days for moxifloxacin cases.

Only 1 TEAE was reported in the cataract study. In 1 besifloxacin case, a mild hypersensitivity/allergic reaction considered possibly related to besifloxacin was reported in the surgical eye. The TEAE resolved after discontinuation of besifloxacin and treatment with medication.

Surgical outcomes were similar between besifloxacin and moxifloxacin cases (Table 3). Unexpected intraocular pressure elevation was reported in 2.7% of besifloxacin and 9.2% of moxifloxacin cases; in these cases, the mean maximum intraocular pressure was 28.9 and 27.1 mm Hg, respectively.

| Table 1. Demographics and Baseline Characteristics of Cataract Cases |
|---------------------------------|----------------|----------------|
| Parameter                        | Besifloxacin  | Moxifloxacin  |
|                                 | (n = 333)     | (n = 152)     | Total (N = 485) |
| Age at the time of surgery, mean (SD), y | 68.2 (10.2) | 68.1 (11.2) | 68.2 (10.5) |
| Sex, n (%)                       |               |               |                |
| Male                             | 146 (43.8)    | 64 (42.1)     | 210 (43.3)     |
| Female                           | 187 (56.2)    | 88 (57.9)     | 275 (56.7)     |
| Surgical eye, n (%)              |               |               |                |
| Right                            | 178 (53.5)    | 73 (48.0)     | 251 (51.8)     |
| Left                             | 155 (46.5)    | 79 (52.0)     | 234 (48.2)     |
| Initial visual acuity, n (%)     |               |               |                |
| 20/60 or worse                   | 151 (45.3)    | 45 (29.6)     | 196 (40.4)     |
| 20/50                            | 35 (10.5)     | 13 (8.6)      | 48 (9.9)       |
| 20/40                            | 51 (15.3)     | 26 (17.1)     | 77 (15.9)      |
| 20/30                            | 44 (13.2)     | 22 (14.5)     | 66 (13.6)      |
| 20/25                            | 28 (8.4)      | 27 (17.8)     | 55 (11.3)      |
| 20/20 or better                  | 24 (7.2)      | 19 (12.5)     | 43 (8.9)       |
| Baseline intraocular pressure, mean (SD), mm Hg | 16.6 (3.2) | 15.6 (1.8) | 16.0 (2.4) |
The final visual acuity was also similar between besifloxacin and moxifloxacin cases (Fig. 1).

**LASIK Study**

The study included 456 cases/eyes (besifloxacin, n = 344; moxifloxacin, n = 112). Four of 7 centers provided both besifloxacin and moxifloxacin cases/eyes, whereas 3 provided besifloxacin cases/eyes only. Demographics were similar across the treatment groups (Table 4). The mean age at the time of the surgery was 37.0 years, and most patients (59.2%) were female. The patients were found to be generally healthy with few comorbid conditions at the time of the surgery. The patients commonly used concomitant topical corticosteroids (99.6%) and artificial tears (98.9%); the use of nonsteroidal antiinflammatory drugs was less common (3.5%). In most of the cases (67.1%), a femtosecond laser was used for apex creation; however, the proportion was significantly larger among moxifloxacin cases (86.6%) than it was among besifloxacin cases (60.8%; P < 0.001). Preoperative corneal thickness, apex thickness, ablation depth, and correction magnitudes were comparable between the treatment groups. Table 5 presents the frequency and the duration of topical antibacterial use. Antibacterials were used preoperatively in 56.4% of besifloxacin cases and in 77.7% of moxifloxacin cases. As was the case with cataract surgery cases, the frequency of preoperative and postoperative dosing was generally lower for besifloxacin than for moxifloxacin. The most common preoperative and postoperative doses used were 3 times daily for besifloxacin and 4 times daily for moxifloxacin. The mean duration of antibacterial use was 8.4 days for besifloxacin cases and 8.3 days for moxifloxacin cases. No TEAEs were reported in the LASIK study. There was no significant difference in the occurrence of unexpected corneal findings between besifloxacin and moxifloxacin cases.
TABLE 4. Demographics and Baseline Characteristics of LASIK Cases

| Parameter                        | Besifloxacin (n = 344) | Moxifloxacin (n = 112) | Total (N = 456) |
|---------------------------------|------------------------|------------------------|-----------------|
| Age at the time of surgery, mean (SD), y | 36.6 (10.5)            | 38.4 (10.6)            | 37.0 (10.5)     |
| Sex, n (%)                      |                        |                        |                 |
| Male                            | 146 (42.4)             | 40 (35.7)              | 186 (40.8)      |
| Female                          | 198 (57.6)             | 72 (64.3)              | 270 (59.2)      |
| Surgical eye, n (%)             |                        |                        |                 |
| Right                           | 172 (50.0)             | 56 (50.0)              | 228 (50.0)      |
| Left                            | 172 (50.0)             | 56 (50.0)              | 228 (50.0)      |
| Initial best-corrected visual acuity, n (%) |          |                        |                 |
| 20/60 or worse                  | 3 (0.9)                | 4 (3.6)                | 7 (1.5)         |
| 20/50                           | 2 (0.6)                | 0 (0.0)                | 2 (0.4)         |
| 20/40                           | 1 (0.3)                | 5 (4.5)                | 6 (1.3)         |
| 20/30                           | 6 (1.7)                | 4 (3.6)                | 10 (2.2)        |
| 20/25                           | 31 (9.0)               | 18 (16.1)              | 49 (10.7)       |
| 20/20 or better                 | 301 (87.5)             | 81 (72.3)              | 382 (83.8)      |

(Table 6). The final visual acuity was similar between besifloxacin and moxifloxacin cases ($P = 0.624$; Fig. 2).

DISCUSSION

In these prospective safety surveillance studies, the perioperative use of besifloxacin ophthalmic suspension 0.6% was not associated with any unique safety concerns in patients undergoing routine primary cataract surgery or LASIK surgery. TEAEs were rare, and surgical outcomes with besifloxacin were similar to those in cases using moxifloxacin ophthalmic solution 0.5%, a fluoroquinolone formulation previously studied in surgical prophylaxis with good tolerability.\textsuperscript{11,12} In addition, final best-corrected visual acuity results were similar with the 2 treatments in both studies.

Although data were collected prospectively, the patients were treated according to the clinician’s usual practice; therefore, the antibacterial use was not randomized, and the perioperative medication regimen varied. In both the studies, perioperative and postoperative dosing frequencies were generally lower for besifloxacin than for moxifloxacin. Although the specifics of intraoperative dosing during LASIK surgery, which was more frequent in the moxifloxacin cases, were not collected, most surgeons report that the standard practice is to give the dose after repositioning of the flap. In both studies, postoperative dosing was most commonly done 3 times daily in the besifloxacin treatment group and 4 times daily in the moxifloxacin treatment group.

Cataract extraction and LASIK are common ocular surgical procedures. As with all ocular surgeries, these procedures are associated with some risk of developing ocular infection. For example, an analysis of Medicare beneficiary claims data estimated the rate of presumed endophthalmitis occurring after cataract surgery at 1.1 cases per 1000 surgeries in 2004.\textsuperscript{13} Similarly, a retrospective study conducted at a single center in Spain estimated the incidence of post-LASIK infectious keratitis at 0.035% per procedure.\textsuperscript{14} Such infections, although relatively rare, are potentially vision-threatening complications of ocular surgery. A number of strategies are recommended to minimize the risk of developing infection for patients undergoing cataract extraction or LASIK, including the use of topical antibiotics in the perioperative period.\textsuperscript{1,2} Although besifloxacin is not approved for this indication, it is often used off-label in this manner, and its use appears to be safe based on these results.

TABLE 5. Frequency and Duration of Topical Antibacterial Use in LASIK Cases

| Perioperative Antibacterial Use | Besifloxacin (n = 344) | Moxifloxacin (n = 112) | $P$     |
|--------------------------------|------------------------|------------------------|---------|
| Preoperative antibacterial dose frequency, n (%) |            |                        |        |
| Did not use                     | 150 (43.6)             | 25 (22.3)              | <0.0001 |
| 1 Time daily                    | 0 (0.0)                | 0 (0.0)                |         |
| 2 Times daily                   | 0 (0.0)                | 0 (0.0)                |         |
| 3 Times daily                   | 138 (40.1)             | 0 (0.0)                |         |
| 4 Times daily                   | 56 (16.3)              | 87 (77.7)              |         |
| >4 Times daily                  | 0 (0.0)                | 0 (0.0)                |         |
| Day of surgery: preoperative instillation frequency, n (%) |            |                        |        |
| Did not use                     | 93 (27.0)              | 76 (67.9)              | <0.0001 |
| 1 Drop                          | 245 (71.2)             | 28 (25.0)              |         |
| 2 Drops                         | 6 (1.7)                | 8 (7.1)                |         |
| 3 Drops                         | 0 (0.0)                | 0 (0.0)                |         |
| 4 Drops                         | 0 (0.0)                | 0 (0.0)                |         |
| >4 Drops                        | 0 (0.0)                | 0 (0.0)                |         |
| Day of surgery: intraoperative instillation frequency, n (%) |            |                        |        |
| Did not use                     | 270 (78.5)             | 69 (61.6)              | 0.0004  |
| 1 Drop                          | 74 (21.5)              | 42 (37.5)              |         |
| 2 Drops                         | 0 (0.0)                | 1 (0.9)                |         |
| 3 Drops                         | 0 (0.0)                | 0 (0.0)                |         |
| 4 Drops                         | 0 (0.0)                | 0 (0.0)                |         |
| >4 Drops                        | 0 (0.0)                | 0 (0.0)                |         |
| Day of surgery: postoperative instillation frequency, n (%) |            |                        |        |
| Did not use                     | 0 (0.0)                | 1 (0.9)                | 0.244   |
| 1 Drop                          | 203 (59.0)             | 74 (66.1)              |         |
| 2 Drops                         | 49 (14.2)              | 33 (29.5)              |         |
| 3 Drops                         | 92 (26.7)              | 3 (2.7)                |         |
| 4 Drops                         | 0 (0.0)                | 0 (0.0)                |         |
| >4 Drops                        | 0 (0.0)                | 0 (0.0)                |         |
| Postoperative antibacterial dose frequency, n (%) |            |                        |        |
| Did not use                     | 0 (0.0)                | 0 (0.0)                | 0.435   |
| 1 Time daily                    | 0 (0.0)                | 1 (0.9)                |         |
| 1 Time daily                    | 0 (0.0)                | 1 (0.9)                |         |
| 3 Times daily                   | 200 (58.1)             | 3 (2.7)                |         |
| 4 Times daily                   | 144 (41.9)             | 107 (95.5)             |         |
| >4 Times daily                  | 0 (0.0)                | 0 (0.0)                |         |
| Duration of antibacterial use, mean (SD), d | 8.4 (3.3) | 8.3 (3.4) | 0.833  |
However, a subsequent study that evaluates the potential of DuraSite suggests that inclusion of DuraSite and moxifloxacin in the ophthalmic surgery setting (cataract surgery and LASIK). 10

Previous preclinical studies evaluating topical antibacterial formulations containing DuraSite reported anterior chamber toxicity after injection of the medications directly into rabbit eyes. 20,21 However, a subsequent study that evaluated topical administration of the DuraSite vehicle to surgically compromised rabbit eyes had no adverse findings. 22

DuraSite is a crosslinked polymer of polyacrylic acid with a molecular weight of $>1 \times 10^6$ Da. 6 Krenzer et al 22 propose that the size and viscoelastic properties of DuraSite facilitate its retention on the ocular surface, leaving little opportunity for the polymer to enter the anterior chamber of the eye through a penetrating wound or LASIK flap. Although the current safety surveillance studies were not powered to detect adverse drug reactions with an incidence of $<0.9\%$, the lack of significant adverse drug reactions with besifloxacin ophthalmic suspension $0.6\%$ in the current and previous safety studies of besifloxacin 17–19 suggests that inclusion of DuraSite in the formulation does not present unique safety concerns in the clinical setting.

In summary, the prophylactic use of besifloxacin ophthalmic suspension $0.6\%$ was associated with no TEAEs in patients undergoing LASIK, and only 1 TEAE in a patient undergoing cataract extraction in these prospective safety surveillance studies. Surgical outcomes with besifloxacin were similar to those achieved with moxifloxacin ophthalmic solution $0.5\%$ for prophylaxis. These findings suggest that safety concerns based on animal models are not supported by clinical data.

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FIGURE 2. The final best-corrected visual acuity (percent of cases) after the LASIK surgery.

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www.corneajrnl.com | 461
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