Once-daily nepafenac ophthalmic suspension 0.3% to prevent and treat ocular inflammation and pain after cataract surgery: Phase 3 study

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PURPOSE: To evaluate once-daily nepafenac 0.3% to prevent and treat ocular pain and inflammation after cataract surgery.

SETTING: Sixty-five centers in the United States and Europe.

DESIGN: Randomized double-masked vehicle- and active-controlled phase 3 study.

METHODS: Patients received nepafenac 0.3% once daily, nepafenac 0.1% 3 times daily, or their respective vehicles from day −1 to day 14 after cataract extraction. An additional drop of study drug was administered 30 to 120 minutes preoperatively. The primary endpoint was the percentage of patients with a cure for inflammation (score of 0 for both aqueous cells and flare) at day 14.

RESULTS: Of randomized patients, 817 received nepafenac 0.3%, 819 received nepafenac 0.1%, and 200 and 206 received the respective vehicles. Significantly more nepafenac 0.3% patients had no inflammation (68.4% versus 34.0%) and were pain free (91.0% versus 49.7%) at day 14 than vehicle patients (both $P<.0001$). Nepafenac 0.3% was noninferior to nepafenac 0.1% for inflammation (95% confidence interval [CI], −5.73% to 3.17%) and pain-free rates (95% CI, −3.08% to 2.70%). At all postoperative visits, fewer treatment failures ($P\leq.0012$) and more clinical successes ($P\leq.0264$) were observed with nepafenac 0.3% versus vehicle. Nepafenac 0.3% was well tolerated and had a safety profile comparable to that of nepafenac 0.1%.

CONCLUSIONS: Once-daily nepafenac 0.3% was noninferior to nepafenac 0.1% 3 times daily for prevention and treatment of ocular inflammation and pain following cataract surgery. The safety of nepafenac 0.3% was comparable to that of nepafenac 0.1%, with the added convenience of once-daily dosing.

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Cataract is the leading cause of blindness worldwide and the main cause of reversible decreased vision in the elderly in the developed world.[1,2] Patients with cataracts have a gradual loss in visual acuity that may be accompanied by reduced physical ability and loss of self-esteem, creating a considerable social and economic burden.[3,4] In developed countries, cataract surgery is one of the most common surgical procedures performed. Overall, its high success rates yield improved visual acuity and improved patient quality of life.[1,5,6] Wider ranging positive effects include a reduced risk for hip fractures in patients who have had cataract surgery compared with matched cataract patients who have not had surgery.[7] As the mean and median age of the world population increases, the prevalence of cataracts and the number of patients in need of cataract surgery will steadily increase worldwide.[1]

Intraocular inflammation is a common event after cataract surgery. It is often managed with corticosteroid and topical antiinflammatory agents to reduce symptoms, increase comfort, and prevent complications.[8,9] The inflammatory process is mediated by the

action of cyclooxygenase (COX) enzymes that lead to the subsequent production of proinflammatory prostaglandins.[8,10] Prostaglandins have in turn been linked to disruption of the blood–aqueous barrier and increases in vascular permeability changes associated with inflammation and edema.[11,12] Nonsteroidal anti-inflammatory drugs (NSAIDs) are potent inhibitors of COX enzymes and prostaglandin production. The efficacy and safety of topical NSAIDs in treating postsurgical ocular inflammation and pain are well established, and the relative merits and risks of NSAIDs versus postoperative topical steroids have been addressed by several authors.[8,10]

Nepafenac ophthalmic suspension 0.1% (nepafenac 0.1%) (Nevanac) is a topical ocular NSAID used to prevent and treat the pain and inflammation associated with cataract surgery.[13,A] In contrast to other ocular NSAIDs, nepafenac is a prodrug that rapidly penetrates the cornea and is deaminated by intraocular hydrolases within ocular tissues to form the active metabolite amfenac.[13,A] Nepafenac and amfenac are potent inhibitors of the COX enzymes COX-1 and COX-2.[14,15] The bioconversion of nepafenac is greatest in vascularized tissues, such as the iris and ciliary body and, to a greater extent, the retina and choroid,[15] the region of the eye with the greatest prostaglandin concentrations and COX activity.[16]

Clinical studies[13,17–19] have shown that nepafenac 0.1% taken 3 times daily beginning the day before surgery is well tolerated and effective in the treatment of the ocular inflammation and pain associated with cataract surgery. Furthermore, recent studies[20,21] have found that nepafenac 0.1% is effective in reducing macular edema secondary to cataract extraction and macular edema associated with diabetes. Nepafenac 0.1% is approved by the European Medicines Agency but not by the United States Food and Drug Administration to reduce the risk for macular edema that can occur after cataract surgery in patients with diabetes.[B]

A new formulation of nepafenac ophthalmic suspension (nepafenac 0.3%) that can be used once a day to prevent and treat ocular inflammation and pain after cataract surgery has been developed and recently approved for use in the U.S.[C] In addition to its higher concentration of the active molecule, nepafenac 0.3% has a reduced particle size compared with nepafenac 0.1%, which increases the surface area for dissolution, and added guar, a retention agent that enhances the bioavailability of nepafenac in the eye over that with nepafenac 0.1%. Here, we report the results of a phase 3 study that evaluated the safety and efficacy of nepafenac 0.3% taken once daily relative to nepafenac 0.1% 3 times daily and the respective vehicles for the prevention and treatment of ocular inflammation and pain 14 days after cataract extraction.

PATIENTS AND METHODS

Study Design

This randomized double-masked parallel-group multicenter vehicle- and active-controlled phase 3 study was performed at 65 centers in Europe (Hungary, Italy, Sweden, and Switzerland) and the United States between June 2010 and May 2011. Eligible patients were randomized (4:4:1:1) to receive nepafenac 0.3% once daily, nepafenac 0.1% 3 times daily, or their respective vehicles.

The study consisted of 6 visits as follows: a screening/baseline visit (performed within 2 days to 6 weeks before the surgery visit), the cataract surgery visit (day 0), and 4 postoperative visits (days 1, 3, 7, and 14). Patients began instilling the study drug—dosed once daily if assigned to nepafenac 0.3% or its vehicle or 3 times daily if assigned to nepafenac 0.1% or its vehicle—into the study eye on the day before cataract surgery (day −1). Dosing continued on the day of surgery (day 0) and for 14 days thereafter. On the day of surgery, designated study personnel instilled 1 additional drop of the assigned study drug into each patient's study eye 30 to 120 minutes before surgery. All patients received the investigator's standard regimen of preoperative, intraoperative, and postoperative care with the exception of NSAID and steroid use. During the study, all patients, investigators, and study-related personnel were masked to the treatment assignment, and all personnel involved in efficacy assessments and analysis of results were masked to the dosing frequency.

The study was performed in accordance with Good Clinical Practices and the ethical principles described in the Declaration of Helsinki. An institutional review board/independent ethics committee in each associated country approved the protocol. On entry, all participating patients provided written informed consent. This study is registered at clinicaltrials.gov as NCT01109173.[D]

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