National PBM Drug Monograph
Nepafenac (Nevanac) Ophthalmic Suspension
July 2006
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

- Nepafenac is the first ocular prodrug nonsteroidal anti-inflammatory drug (NSAID). It is converted to amfenac by intraocular hydrolases. Amfenac is a cyclooxygenase inhibitor, which decreases prostaglandin production, and therefore decreases inflammation.

- Nepafenac received FDA Priority Approval (significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease) on August 19, 2005. Nepafenac is approved for the treatment of pain and inflammation associated with cataract surgery. Inflammation often occurs after intraocular surgery. Anti-inflammatory therapies are often used to reduce inflammation and prevent further complications such as cystoid macular edema (CME). Corticosteroids are effective at reducing inflammation, however have many side effects. NSAIDs are an alternative option.

- There are thought to be several advantages of nepafenac compared to other topical NSAIDs, however these advantages are from published studies in animals or unpublished studies in humans. During non-clinical studies in rabbits, nepafenac was shown to penetrate the cornea at a faster rate, provide more complete and longer lasting inhibition of prostaglandin synthesis and vascular permeability than diclofenac. However, these published studies were not done in humans and these endpoints were not studied in the clinical trials. Nepafenac is also thought to cause less ocular burning and stinging. An unpublished study comparing nepafenac to diclofenac in healthy human subjects demonstrated less ocular irritation and burning with nepafenac compared to diclofenac.

- There are a total of 5 studies in humans examining the use of nepafenac after cataract surgery, however none are currently published. The only published study in humans evaluated the efficacy and safety of nepafenac ophthalmic suspension compared to diclofenac for the treatment of postoperative pain and photophobia in patients undergoing excimer photoreactive keratectomy (PRK). All information contained in this monograph came from Data on File from Alcon Laboratories or the AMCP Managed Care Dossier and the study done in humans during PRK surgery. The studies from the managed care dossier consist of one pivotal trial, one efficacy and safety trial, two dose-response trials, and one trial comparing the safety and tolerability of nepafenac to diclofenac. All of the cataract surgery studies, except the nepafenac/diclofenac study, used aqueous cells and flare (signs of ocular inflammation) as the basis for evaluating the efficacy of the drug product. The study duration for all was 16 days. Nepafenac ophthalmic suspension at several different doses appeared to be safe and efficacious compared to placebo.

- Overall, the unpublished data have shown nepafenac to be safe. No deaths have been reported in any of the nepafenac treatment groups. There have been very few serious adverse events reported in the nepafenac treatment groups and most of then were not thought to be treatment related. Overall, the most commonly reported adverse events (AEs) in the nepafenac treatment groups were decreased visual acuity (4.2%) and capsular opacity (2.9%). The reviewing FDA Medical Officer concluded that there were no unexpected adverse events with nepafenac. Most events were non serious, mild to moderate in intensity and resolved with or without treatment.[11] The reviewer concluded that the benefit of nepafenac outweighed the risk.

Introduction

The purposes of reviewing nepafenac are to (1) evaluate the evidence on safety, efficacy, and cost (2) to examine if nepafanac would be a beneficial addition to the VA formulary, (3) to define its role in ophthalmic therapy, and (4) identify patient's that would receive maximum benefit from nepafanac.

Pharmacology/Pharmacokinetics

Nepafanac is a sterile, topical, nonsteroidal anti-inflammatory and analgesic prodrug. Nepafenac comes as a 0.1% suspension and each ml contains 1mg of nepafenac.[1]

Nepafenac is the first prodrug nonsteroidal anti-inflammatory drug (NSAID). Once nepafanac is administered in the eye, it penetrates the cornea and distributes to all intraocular compartments and tissues including the aqueous humor, iris, ciliary body, retina, and choroid. Once nepafenac reaches the tissues previously mentioned, it is converted by ocular hydrolysis to amfenac, which is the active NSAID.[2] Amfenac inhibits prostaglandin H synthase which is an enzyme responsible for converting cyclooxygenase into prostaglandins (inflammatory mediators). Nepafenac targets the anterior segment of the eye, intraocular, and vascularized tissues.[2,3]

The onset of action is around 15 minutes and duration of action is 8 hours after topical ocular administration. Small quantifiable plasma concentrations of nepafenac and amfenac have been observed in subjects 2-3 hours after topical administration. After ocular administration the mean steady-state Cmax of nepafenac and amfenac were 0.310 +/- 0.014 ng/ml and 0.422 =/- 0.121 ng/ml, respectively.[3]

After oral administration of nepafenac in rats, nepafenac was eliminated in urine (57%) and fecal (40%) routes over 7 days.

Half-lives of radioactivity in the conjunctiva, cornea, and iris/ciliary body of nepafenac ophthalmic solution are 14-20 hours.[3] No information is available on tmax, AUC, Vd, or, Cl.

The above information came from Data on file from Alcon Labs or form in vitro data from pharmacokinetic studies.

FDA Approved Indication(s) and Off-label Uses [3,4,5]

Nepafenac is indicated for the treatment of pain and inflammation associated with cataract surgery. Nepafenac was approved on August 19, 2005 as a priority drug approval.

It is also being studied for the relief of pain and photophobia associated with photorefractive surgery, and retinal edema secondary to diabetic retinopathy, however results of these studies have not been presented or published.

Current VA National Formulary Alternatives [3,6,7]

Often in clinical practice NSAIDs are used concurrently with steroids. There are three topical NSAIDs approved for the treatment of postoperative inflammation (bromfenac sodium 0.1% (Xibrom), ketorolac tromethamine ophthalmic solution 0.5% (Acular), dicolfenac sodium ophthalmic solution 0.1% (Voltaren) and two topical ophthalmic steroids approved for the treatment of postoperative inflammation (loteprednol etabonate ophthalmic solution 0.5% (Lotemax), and rimexolone ophthalmic suspension 1% (Vexol)).

Currently the national formulary has 2 topical NSAIDs:

(1) Ketorolac tromethamine ophthalmic solution, FDA approved for postoperative inflammation in patients who have undergone cataract extraction and temporary relief of ocular itching due to seasonal allergic conjunctivitis as well as postoperative pain and photophobia associated with corneal refractive surgery.

(2) Diclofenac sodium ophthalmic solution, FDA approved for treatment of postoperative inflammation in patients who have undergone cataract extraction and for temporary relief of pain and photphobia in patients undergoing corneal refractive surgery.

Dosage and Administration[1,3]

The current recommended dose is nepafenac 0.1% suspension one drop applied to the affected eye(s) three times a day beginning day 1 prior to cataract surgery, continued on the day of surgery, and throughout the first 2 weeks postoperatively. Nepafenac may also be administered with other topical ophthalmics including beta blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. Nepafenac should be shaken well before using and can be stored at temperatures of 2-25 degrees Celsius (36-77 degrees F).

Efficacy

Efficacy Measures

The FDA approval of nepafenac was based on a total of 5 studies, none of which have been published. The only published study was done in patients undergoing PRK surgery. The cataract surgery studies consisted of one pivotal trial (C-03-32), one efficacy and safety study (C-02-53), two dose-response studies (C-95-93 and C-97-30), and one trial comparing the safety and tolerability of nepafenac to diclofenac (C-95-91). All of the studies (except C-95-91) used aqueous cells and flare (signs of ocular inflammation) as the basis for evaluating the efficacy of the drug product. The standard in ophthalmic practice is to use aqueous cells and flare to evaluate inflammation and this is done using slit-lamp biomicroscopy. Aqueous cells were graded using a 5-point scale and aqueous flare was graded by 4-point scale. These scales have been used in the past to assess post-cataract inflammation in clinical trials. The lower the score, the lower the inflammation.[5] Trials C-95-93 and C-97-30 used aqueous cell flare scores as the primary efficacy endpoint. Trial C-02-53 used treatment failures (which are based on aqueous cells and flare scores) and ocular pain scores as the primary efficacy measure. Treatment failure was defined as a grade 3 or higher cells or flare score and Grade 4 or greater pain score. Trial C-03-32 used the percentage of cures (absence of inflammation, cells + flare = 0) as the primary efficacy endpoint. Two efficacy studies (C-02-53 and C-03-32) also evaluated ocular pain on a 6-point scale. Trial C-95-91 was done in healthy adults and measured ocular discomfort composite score, membrane discomfort composite score, and visual clarity and burning profile.[3,4,5] The was very little information available on the specifics of the C-95-91 study.

Summary of efficacy findings

For further details on the efficacy results of the clinical trials, refer to

Appendix: Clinical Trials

In the unpublished efficacy studies (C-02-53 and C-03-32), patients were randomized to receive 1) nepafenac 0.1% at different dosing schedules of 1 drop daily, 1 drop twice daily, 1 drop three times a day, or placebo given with the three above dosing regimens, or 2) nepafenac 0.1% 1 drop three times a day versus placebo. The results of study C-02-53 (3 different dosing schedules) demonstrated that TID regimen proved to be more efficacious than nepafenac given daily or BID, based upon the percent of treatment failures (TID 19.6% versus daily 25% versus BID 30%). However nepafenac 0.1% administered 1-drop daily, bid, and tid was superior to placebo in the treatment of inflammation and pain associated with cataract surgery based on aqueous cells and pain assessment. In both of the efficacy studies, patients receiving nepafenac had a statistically significant difference in percentage of patients that were pain free at days 1,3,7, and 14 postoperatively compared to placebo. (C-02-53: post op day 1, 3, 7, and 14, $p=0.0023$, $p=0.002$, $p<0.001$, $p<0.001$, respectively; C-03-32: $p<0.001$ for post op days 1, 3, 7, and 14)

The two unpublished, dose response studies (C-95-93 and C-97-30) examined the mean changes from baseline in aqueous cell score, aqueous flare score, and cells + flare score. Study C-95-93 used nepafenac 0.03%, 0.1%, 0.3%, and placebo. Study C-97-30 used nepafenac 0.003%, 0.01%, 0.03%, and 0.1%. All of the strengths in both studies were safe and efficacious in the treatment of inflammation associated with cataract surgery and IOL implantation.[3,4,5] (If you refer to the Appendix (C-97-30), it is unclear where the evidence for using 0.1% came from considering 0.1% had the least percentage cures and a lower difference in mean cells score change from baseline.

All values were statistically significant, however it is difficult to know what the clinical significance is from the smaller difference from baseline.)

In unpublished study C-95-91, there was a significant difference of less ocular discomfort with nepafenac compared to diclofenac and significantly less burning with nepafenac than with diclofenac.[3] This study did not provide statistics or specifics on how the study was conducted.

The published study evaluating the efficacy and safety of nepafenac ophthalmic suspension 0.03% and 0.1% for the treatment of postoperative pain and photophobia found nepafenac 0.03% and 0.1% to be effective for treatment of pain and photophobia in patients undergoing excimer photoreactive keratectomy (PRK). It was a 7-day randomized, double-masked, parallel group trial and patients were randomly assigned to received nepafenac 0.03% or 0.1% or diclofenac sodium ophthalmic solution 0.1%. The dose regimen for all 3 treatments was the same: day 0 (surgery): 2 drops in operative eye 1 hour before surgery and then 2 drops after surgery; 1 drop 4 hours after first post op dose, then 1 drop 8 hours after first postoperative dose, day 1 (day after surgery): 1 drop four times a day. After the day after surgery dose was completed, the drug was discontinued. Patients recorded their pain and photophobia from day 0 through day 2 rating their pain using a visual analog scale and photophobia on a categoric scale. Sixty patients were enrolled (20 patients per group) in this study and no differences were found between the three groups on pain scores on the day of surgery. Three hours after surgery the nepafenac 0.03% group had significantly higher mean pain scores than the nepafenac 0.1% group ($p<0.038$). On day 2, the nepafenac 0.1% patients had less pain than the diclofenac 0.1% patients ($p<0.024$). No serious adverse events were reported in this study. There were two adverse events related to treatment that occurred: a corneal infiltrate in 1 patient in the nepafenac 0.03% group and ocular discomfort in the nepafenac 0.1% group. This information came from the study abstract and no thorough clinical trial review has been completed.[8]

Adverse Events (Safety Data)[3,4,5]

Deaths and Other Serious Adverse Events (AEs)

- No deaths have been reported in any of the nepafenac treatment groups. There have been very few serious adverse events reported in the nepafenac treatment groups.
- Serious AEs reported in Studies C-03-32 and C-02-53 consisted of encephalitis in a placebo patient and aphasia in a nepafenac 0.1% BID patient. These were not thought to be treatment related.
- Serious AEs reported in Studies C-95-93 and C-97-30 consisted of pancreatitis, gastritis, nausea and vomiting, decreased weight loss, intestinal obstruction, and sepsis in the nepafenac treatment groups and were not thought to be treatment related. Serious AEs seen in the placebo group were hypopyon, ocular pain, and uveitis.

Common Adverse Events

The most frequently reported ocular adverse events were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. It was not specified if these were temporary or permanent adverse events.

The most common AEs occurring in all 4 of the efficacy/placebo studies are listed in the table below. [1]

Table 1 Common Adverse Events

Adverse Event	Nepafenac 0.1% (n=518) N (%)	Placebo (n=410) N (%)
Decreased Visual Acuity	22 (4.2%)	14 (3.4%)
Capsular Opacity	15 (2.9%)	12 (2.9%)
Photophobia	3 (0.6%)	23 (5.6%)
Foreign Body Sensation	11 (2.1%)	15 (3.7%)
Ocular Hyperemia	3 (0.6%)	21 (5.1%)
Conjunctival Edema	6 (1.2%)	7 (1.7%)

Ocular Pruritis	8 (1.5%)	11 (2.7%)
Adverse Event	**Nepafenac 0.1% (n=518)** **N (%)**	**Placebo (n=410)** **N (%)**
Ocular Pain	3 (0.6%)	8 (2.0%)
Ocular Discomfort	4 (0.8%)	6 (1.5%)
IOP Increased	6 (1.2%)	3 (1.7%)
Dry Eye	3 (0.6%)	3 (0.7%)
Corneal Edema	3 (0.6%)	4 (1.0%)
Tearing	3 (0.6%)	4 (1.0%)
Vitreous Disorder	4 (0.8%)	1 (0.2%)
Conjunctivitis	2 (0.4%)	4 (1.0%)
Corneal Striae	1 (0.2%)	5 (1.2%)
Vision Blurred	2 (0.4%)	4 (1.0%)
Ititis	2 (0.4%)	3 (0.7%)
Vitreous Detachment	4 (0.8)	1 (0.2%)
Corneal Abrasion	2 (0.4%)	2 (0.5%)
Lid Margin Crusting	3 (0.6%)	1 (0.2%)
Sticky Sensation	3 (0.6%)	_
Macular Edema	_	3 (0.7%)
Ocular Irritation	_	2 (0.5%)
Precipitate Pigment IOL	_	2 (0.5%)

Adapted from Managed Care Dossier, Data on file – Alcon Labs

The numbers and percentages listed above are the overall number of patients experiencing the event. Most of the AEs listed above were non-treatment related. Some of these events could have been a result of the surgery. Headache, hypertension, nausea/vomiting, and sinusitis were nonocular adverse events that occurred around 1-4%.[I]

Precautions/Contraindications[1,3,4]

Precaution should be used in any patient that has had sensitivity to acetylsalicylic acid, phenyacetic acid derivatives and other NSAIDs because there is the potential for cross-sensitivity

Precautions

- NSAIDs may delay healing from surgery and concurrent use of nepafenac with steroids could slow healing even more. Use of some topical NSAIDs may result in keratitis, and in susceptible patients may result in epithelial breakdown, corneal thinning, corneal erosion, and corneal ulceration. Patients who have any evidence of epithelial breakdown should immediately stop using nepafenac and should be monitored.
- Nepafenac should be used with caution in patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface disease, rheumatoid arthritis, or repeat ocular surgeries within a short period of time.
- Nepafenac should be used with caution in patients with known bleeding tendencies or who are receiving other medications that may prolong bleeding time.
- Use of topical NSAIDs for use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk of corneal adverse events.

- Nepafenac has not been studied in long term carcinogenicity studies, however amfenac sodium was given to mice at doses of 30mg/kg/day and was shown to be non-carcinogenic.

Pregnancy and Lactation[3]

Pregnancy Category C: Nepafenac has not been studied in humans in pregnancy or in pediatric patients. There were reproduction studies done in rabbits and rats receiving oral doses of nepafenac up to 10mg/kg/day. This revealed no evidence of teratogenicity, however it did cause maternal toxicity. In rats, nepafenac has been shown to cross the placental barrier. Nepafenac should be avoided in late stages of pregnancy because of the known effects of prostaglandin biosynthesis inhibiting drugs in the fetal cardiovascular system.

Contraindications

Nepafenac is contraindicated in patients who have previously had a hypersensitivity to other NSAIDs or any other component in the nepafenac formulation.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

LA/SA for trade name Nevanac:

Potential name confusion: Neo-Dex (ophthalmic solution)

Potential severity: Moderate

Probability: Frequent

Look-alike / Sound-alike (LA / SA) Error Risk Potential (continued)

Potential name confusion: Valnac cream (beclometasone cream)

Potential Severity: Moderate

Probability: Uncommon

Potential name confusion: Nolvadex (tamoxifen tablets)

Potential severity: Moderate

Probability: Remote

Potential name confusion: Kinevac (sincalide) Kinevac is a diagnostic agent given by injection to check if the gallbladder and pancreas are working.

Potential severity: Moderate

Probability: Uncommon

Potential name confusion: Navane (thiothixene)

Potential severity: Moderate

Probability: Remote

LA/SA for generic nepafenac:

Potential name confusion: Bromfenac sodium (Xibrom ophthalmic)

Potential severity: Moderate

Probability: Occasional

Potential name confusion: Naprapac (part of a Prevacid Naprapac)

Potential severity: Moderate

Probability: Remote

Potential name confusion: Mefenamic acid (Ponstel)

Potential severity: Moderate

Probability: Uncommon

Drug Interactions[1]

Drug-Drug Interactions

Drug-drug interactions involving the CYP-mediated metabolism system of drugs is unlikely because in vitro metabolism of other drugs metabolized by the CYP P450 system did not show any drug interactions. This was done in concentrations of 300ng/ml of nepafenac. Protein binding drug-drug interactions are also unlikely.

Drug-Lab Interactions

There are no relevant drug-lab interactions.

Acquisition Costs

Table 2 Cost Comparison of Ocular NSAIDs

Drug	Pre-op Dose	Post-op dose	Total number of drops	Cost/ml ($)	Cost/Treatment/patient ($)
Nepafenac 0.1% 3ml	1 drop TID 1 day prior to cataract surgery and on day of surgery	1 drop TID for the first 2 weeks of post-op period	48	6.32	18.98
Diclofenac 0.1% 5ml		1 drop QID beginning 24 hours after surgery	56	1.33	6.63
Ketorolac 0.4% 5ml		1 drop QID for up to 4 days	16	7.83	39.13
Ketorolac 0.5% 3ml		1 drop QID starting 24 hours after surgery, continuing up to 2 weeks	56	7.61	22.85
Ketorolac 0.5% 5ml		1 drop QID starting 24 hours after surgery, continuing up to 2 weeks	56	7.60	38.00

Costs: VA costs as of 3/2/06

Usage of Ocular NSAIDs in VHA

FY 2005

VA Product	Total Rxs	Day30Rxs	Unique Patients
DICLOFENAC NA 0.1% SOLN,OPH	5,371	6,338	2,923
KETOROLAC TROMETHAMINE 0.4% SOLN,OPH	1,298	1,370	652
KETOROLAC TROMETHAMINE 0.5% (PF) SOLN,OPH,0.4ML	10	10	7
KETOROLAC TROMETHAMINE 0.5% SOLN,OPH	38,459	43,691	18,104
NEPAFENAC 0.1% SUSP,OPH			

Conclusions

Nepafenac is FDA approved for the treatment of pain and inflammation associated with cataract surgery. It received Priority Review from the FDA, which is defined as significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. Nepafenac is the first and only topical NSAID prodrug. Once it

reaches the iris/ciliary body/retina, nepafenac is converted to its active form, amfenac and it is thought that this leads to sustained suppression of cyclooxygenase activity in vascularized portions of the eye. It is thought that nepafenac is able to penetrate the cornea and distribute to all intraocular compartments and tissues including the aqueous humor, iris, ciliary body, retina, and choroid more than other topical NSAIDs. An in vitro study done in rabbits showed that diclofenac administered topically penetrated intraocular tissues at a slower rate than nepafenac and leaves higher concentrations on the surface of the eye.[2] This could potentially lead to a slower rate of penetration, which could correlate with decreased intraocular efficacy, however this has yet to be determined. The potential benefit of nepafenac to penetrate posterior parts of the eye could result in a greater therapeutic response; however it is unknown what the clinical significance of increased penetration of nepafenac will be. This has not been studied in human clinical trials. There have not been any head- to- head efficacy studies comparing nepafenac to other topical ocular NSAIDs. (The C-95-91 study was comparing the safety and tolerability of nepafenac to diclofenac.)

Overall, the conclusions for the unpublished clinical trials that support the efficacy and safety of nepafenac ophthalmic suspension are:

- Nepafenac 0.1% suspension given TID is effective in the *prevention* of inflammation caused by cataract surgery. In Study C-03-32, there was a statistically significant greater percentage of cures compared to placebo on Days 1 and 3 (p values: p=0.005 and p=0.0012, days 1 and 3 respectively).
- Nepafenac 0.1% suspension given TID is effective in the *treatment* of inflammation caused by cataract surgery. In studies C-03-32 and C-02-53, there was a statistically significant greater percentage of cures, lower incidence of clinically significant inflammation, reduction in aqueous cells, aqueous flare, and aqueous cells + flare scores, and reduction in the incidence of treatment failures compared to placebo (See Appendix p. 10-12).
- Nepafenac 0.1% suspension given TID is more efficacious than given once daily or BID in the prevention and treatment of pain and inflammation after cataract surgery as shown in Study C-02-53 by earlier efficacy (percent treatment failures and aqueous cells score). (See Appendix p.10)
- Nepafenac suspension concentrations ranging from 0.003% to 0.3% (0.003%, 0.01%, 0.03%, 0.1%, and 0.3%) were shown to be efficacious in the treatment of inflammation due to cataract surgery. In studies C-95-93 and C-97-30, there was a statistically significant greater reduction from baseline of aqueous cells, aqueous flare, and aqueous cells + flare scores, greater percentage of cures, reduction in incidence of treatment failures compared to placebo (See Appendix p.12-14)
- Nepafenac 0.1% suspension given TID was shown to be effective for the prevention and treatment of ocular pain after cataract surgery. In studies C-02-53 and C-03-32, there was a statistically significant greater incidence of patients who were pain free compared to placebo on each individual post operative day of 1,3,7, and 14 and all post operative days combined (see Appendix p. 10-12).
- Nepafenac 0.1% to 0.3% suspension was better tolerated than diclofenac 0.1%. In study C-95-91, there was a statistically significant difference of less ocular discomfort compared with diclofenac and significantly less burning with nepafenac than with diclofenac (see Appendix p.15).
- The overall safety profile of nepafenac included a total of 1,371 patients who received at least one dose of study medication. A total of 907 patients were exposed to nepafenac suspension. It appeared to be safe and well tolerated in patients undergoing cataract surgery and intraocular lens implantation (IOL). Adverse events were nonserious, generally mild to moderate in intensity, usually resolved with or without treatment, and were not attributed to the study drug. There were more patients in the placebo group that experienced AEs compared to the treatment group and the rate of study discontinuation due to AEs was greater in the placebo group.[3] However, there are no specific data on ADRs and since studies have not been published, it is difficult to evaluate the safety of nepafenac. However, the reviewing FDA Medical Officer concluded that there were no unexpected adverse events with nepafenac. Most events were non serious, mild to moderate in intensity and resolved with or without treatment.[11] The reviewer concluded that the benefit of nepafenac outweighed the risk.

The acquisition cost of nepafenac is comparable to other available ocular NSAIDs. Nepafenac is less expensive than ketorolac. Diclofenac is less expensive than nepafenac, however in one unpublished study, diclofenac had more ocular irritation and burning than nepafenac, which may outweigh the cost benefit of diclofenac.

References:

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Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to December 2005) using the search terms nepafenac and Nevanac. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. There are currently no published randomized controlled trials, so all of the clinical evidence presented came from the AMCP dossier.

Citation	Stewart WC, Stewart R, Maxwell WA, Markwardt K, Disbrow D. Pre- and Post-operative Clinical Posology Evaluation of Nepafenac Ophthalmic Suspension, 0.1% for Anterior Segment Inflammation after Cataract Surgery. (Unpublished study **C-02-53)**.
Study Goals	To evaluate the safety and efficacy of nepafenac ophthalmic suspension for treatment of inflammation in patients requiring cataract extraction with intraocular lens implantation.
Methods	**Study Design** ***Design***: Multicenter, randomized, double-blind, placebo-controlled, parallel-group study ***Treatment groups***: 220 patients randomly assigned to: ➢ Nepafenac ophthalmic suspension 0.1% in affected eye 1 drop daily (n=50) ➢ Nepafenac ophthalmic suspension 0.1% in affected eye 1 drop twice daily (n=53) ➢ Nepafenac ophthalmic suspension 0.1% in affected eye 1 drop three times daily (n=58) ➢ Vehicle/placebo dosed as 3 different schedules above (daily, bid or tid) (n=59) ***Length of study***: 16 days (dosing began 1 day prior to surgery and continued on day of surgery through first 2 weeks of postoperative period) ***Efficacy measures used:*** ➢ **Primary**: Treatment failures (cells score ≥ 3, flare score =3, or ocular pain score ≥ 4) Efficacy variables were measured at Day 1, 3, 7, and 14 postoperatively. ➢ **Secondary**: mean aqueous cells score, mean flare score, and mean inflammation score (cells + flare), clinically significant inflammation (cells + flare ≥ 4), and percent of treatment responders (cells ≤ 1 and flare = 0) **Data Analysis** ➢ Post hoc analysis: for percent cures (defined as cells + flare score = 0), for percent clinical success (0-5 cells [grade 0-1] + flare), for percent pain free ➢ Intention-to-treat analysis (212 patients included)
Criteria	**Inclusion criteria** ➢ Men of women of any gender ≥ 18 years of age ➢ Individuals who had a cataract and were expected to undergo cataract extraction with the implantation of a posterior chamber intraocular lens **Exclusion criteria** ➢ Any intraocular inflammation or ocular pain greater than Grade 1 in the study eye that was present during the screening slit-lamp examination ➢ Previous ocular trauma to the operative eye; planned multiple procedures during cataract/IOL implantation surgery ➢ Presence of congenital or ocular anomaly ➢ Nonfunctional fellow eye ➢ History of chronic or recurrent inflammatory eye disease (iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis) ➢ Known or suspected allergy or hypersensitivity to NSAIDs or any component of study medication ➢ Use of topical ocular or systemic steroids within 14 days prior to surgery ➢ Use of topical ocular or systemic NSAIDs within 7 days of surgery, except and allowed daily dose of 81mg baby aspirin ➢ Pregnant or lactating women ➢ Proliferate diabetic retinopathy (operative eye), uncontrolled diabetes mellitus ➢ Participation in any other clinical study within 30 days prior to surgery

Results

Data analysis

Summary of Non-Pain Related Efficacy Results

(All values reported for post op day 14 unless otherwise stated)

Efficacy Parameter	NEP 0.1% daily (n=48)	NEP 0.1% BID (n=50)	NEP 0.1% TID (n=56)	Placebo (n=58)	p-value placebo vs. TID
% Treatment Failures	25%	30%	19.6%	60.3%	<0.0001
Mean Cells Score (units)	1.1	1.2	0.9	2.0	<0.0001
Mean Flare Score (units)	0.4	0.6	0.4	1.1	<0.0001
Mean cells + Flare Score (units)	1.6	1.8	1.3	3.1	<0.0001
% Clinically Significant Inflammation	20.8	22.0	14.3	53.4	<0.0001
% Cures (cumulative)	47.9	46.0	46.4	22.4	0.0092
% Clinical Success (cumulative)	56.3	56	66.1	32.8	<0.0001

Pain Related Efficacy Results

Efficacy Parameter	Postop. Day	NEP 0.1% TID (n=56)	Placebo (n=58)	P-Value
% Pain free	1	80.4%	53.4%	0.0023
	3	85.7%	53.4%	0.0002
	7	92.9%	53.4%	<0.0001
	14	98.2%	62.1%	<0.0001
% Pain free at all visits	1-14	76.8%	39.7%	<0.0001

Tables adapted from Nepafenac Dossier

Safety:

The AEs that occurred in the safety population (n=220) were overall nonserious, mild to moderate in intensity, usually resolved and generally did not cause discontinuation from the study. There was one treatment related AE of ocular pain in a patient in the nepafenac BID treatment group and one patient receiving nepafenac daily experienced a treatment related AE (bilateral choroidal effusion) which led to discontinuation from the study.

Conclusions

Nepafenac ophthalmic suspension 0.1% dosed daily, BID, or TID is effective, well tolerated, and safe for the treatment of inflammation associated with cataract surgery and IOL implantation. The most effective dosing regimen was nepafenac 0.1% TID for preventing the incidence of treatment failures and decreasing inflammation.

Critique

Strengths

- Used intention to treat analysis and showed distribution of patients excluded from analysis.
- Fairly large population.
- Used appropriate endpoints.

Limitations

- Not a peer reviewed published trial, all information came from Dossier.
- Only compared TID dosing to placebo.

<table>
<tr><td>Citation</td><td>Lane SS, Modi SS, Holland EJ, Markwardt K, Sager D. Pre- and Post-operative Nepafenac Ophthalmic Suspension, 0.1% for Anterior Segment Inflammation after Cataract Surgery. (Unpublished study C-03-32).</td></tr>
<tr><td>Study Goals</td><td>To evaluate the safety and efficacy of nepafenac suspension for reducing pain and inflammation in patients requiring cataract extraction and intraocular lens implantation.</td></tr>
<tr><td>Methods</td><td>Study Design
Design: multicenter, randomized, double-blind, placebo-controlled, parallel-group study
Treatment groups: 487 patients were randomly assigned to:
➢ Nepafenac 0.1% one drop TID (n=247)
➢ Vehicle/placebo (n=240)
Both treatments were administered as 1 drop in the affected eye TID starting 1 day prior to surgery, the day of surgery, and continuing for 14 days (post op)
Length of study: 16 days
Efficacy measures used:
➢ Primary: percent cures (defined as cells + flare score = 0) at day 14
➢ Secondary: Percent treatment failures (cells score ≥ 3, flare score = 3, or ocular pain score ≥ 4),
➢ Percent pain free, Clinically significant inflammation (cells + flare score ≥ 4)
Data Analysis
➢ Post hoc analysis was used to assess percent clinical success
➢ Intention-to-treat analysis were preformed</td></tr>
<tr><td>Criteria</td><td>Inclusion criteria
➢ Men of women of any gender ≥ 18 years of age
➢ Individuals who had a cataract and were expected to undergo cataract extraction with the implantation of a posterior chamber intraocular lens
Exclusion criteria
➢ Any intraocular inflammation or ocular pain greater than Grade 1 in the study eye that was present during the screening slit-lamp examination
➢ Previous ocular trauma to the operative eye; planned multiple procedures during cataract/IOL implantation surgery
➢ Presence of congenital or ocular anomaly
➢ Nonfunctional fellow eye
➢ History of chronic or recurrent inflammatory eye disease (iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis)
➢ Known or suspected allergy or hypersensitivity to NSAIDs or any component of study medication
➢ Use of topical ocular or systemic steroids within 14 days prior to surgery
➢ Use of topical ocular or systemic NSAIDs within 7 days of surgery, except and allowed daily dose of 81mg baby aspirin
➢ Pregnant or lactating women
➢ Proliferate diabetic retinopathy (operative eye), uncontrolled diabetes mellitus
➢ Participation in any other clinical study within 30 days prior to surgery</td></tr>
<tr><td>Results</td><td>Data analysis (all values reported for postop. day 14)
<table>
<tr><th>Efficacy Parameter</th><th>NEP 0.1% TID (n=243)</th><th>Placebo (n=233)</th><th>P-value</th></tr>
<tr><td>% Cures</td><td>62.6</td><td>17.2</td><td><0.0001</td></tr>
<tr><td>% Treatment Failures</td><td>8.2</td><td>60.9</td><td><0.0001</td></tr>
<tr><td>% Clinical Success (cumulative)</td><td>81.9</td><td>25.3</td><td><0.0001</td></tr>
<tr><td>% Pain free</td><td>93</td><td>45.1</td><td><0.0001</td></tr>
</table>
Pain Related Efficacy Results
<table>
<tr><td>Efficacy Parameter</td><td>Postop. Day</td><td>NEP 0.1% TID (n=243)</td><td>Placebo (n=233)</td><td>P-Value</td></tr>
<tr><td>% Pain free</td><td>1</td><td>83.1%</td><td>41.6%</td><td><0.001</td></tr>
<tr><td></td><td>3</td><td>90.9%</td><td>46.4%</td><td><0.001</td></tr>
<tr><td></td><td>7</td><td>89.3%</td><td>44.2%</td><td><0.001</td></tr>
<tr><td></td><td>14</td><td>93.0%</td><td>45.1%</td><td><0.001</td></tr>
</table>
Tables adapted from Nepafenac Dossier

Safety:</td></tr>
</table>

	Overall, adverse events (AEs) in the safety population (n=487) were nonserious, mild or moderate in intensity, usually resolved, and generally did not cause discontinuation from the study. No treatment related events or deaths were associated with nepafenac suspension and no patients withdrew from the study for serious adverse events. One nepafenac patient and six placebo patients discontinued the study for mild to moderate AEs considered to be unrelated to the study drug.
Conclusions	Nepafenac suspension 0.1% administered TID appeared to be effective, well tolerated, and safe for the treatment and prevention of pain and inflammation associated with cataract surgery and IOL implantation.
Critique	**Strengths** ➢ Used intention to treat analysis and showed distribution of patients excluded from analysis. ➢ Had large study population. ➢ Used appropriate endpoints **Limitations** ➢ Not a peer reviewed published clinical trial.

Citation	NEVANAC (nepafenac ophthalmic suspension 0.1%) Managed Care Dossier. *Data on file*. **C-95-93.**
Study Goals	To evaluate the efficacy of nepafenac suspension (0.03%, 0.1% and 0.3%) for the treatment of inflammation in patients requiring cataract surgery.
Methods	**Study Design** ***Design:*** multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose response study ***Treatment groups:*** (n=280) ➢ Nepafenac 0.03% (n=70) ➢ Nepafenac suspension 0.1% (n=70) ➢ Nepafenac 0.3% (n=68) ➢ Vehicle/placebo (n=72) All treatments were given as 1 drop in the affected eye QID beginning 1 day after surgery and continuing for 14 days postoperatively (total of 14 days) ***Length of study:*** 14 days ***Efficacy measures used: (measured at day 1,4,8,and 15 post operatively)*** ➢ **Primary:** Mean change from baseline in aqueous cell score, Mean change from baseline in aqueous flare score, Mean change from baseline in cells + flare score ➢ **Secondary:** Percent cures (cells + flare score = 0) at day 15, Percent treatment failures (cells + flare score ≥ baseline score) **Data Analysis** ➢ Intention to treat analysis was preformed. ➢ P< 0.05 was considered to be statistically significant
Criteria	**Inclusion criteria** ➢ Men of women of any gender ≥ 18 years of age ➢ Individuals who had a cataract and were expected to undergo cataract extraction with the implantation of a posterior chamber intraocular lens ➢ Clinically significant inflammation (cells + flare score ≥ 4 and a flare score ≥ 2 units) on Day 1 post surgically **Exclusion criteria** ➢ Surgical complications ➢ Previous cataract extraction or IOL implantation ➢ Nonfunctional eye ➢ History of chronic or recurrent inflammatory eye disease ➢ Hypersensitivity to NSAIDs or any component of study medication ➢ Topical ocular or systemic corticosteroids w/in 30 days, or NSAIDs w/in 14 days

Results

Data analysis (all values reported for ITT values for study endpoint, postop. day 15)

Efficacy Parameter	NEP 0.03% QID (n=70)	NEP 0.1% QID (n=70)	NEP 0.3% QID (n=68)	Placebo (n=72)
Mean cells score change from baseline	-1.77*	-1.71*	-1.67*	-1.38
Mean flare score change from baseline	-1.65*	-1.71*	-1.67*	-1.20
Mean cells + flare score change from baseline	-3.42*	-3.42*	-3.34*	-2.58
% cures	34.3%*	32.9%*	26.5%	18.1%
% treatment failures	1.4%*	2.9%*	1.5%*	13.9%

* indicates statistically significant ($p<0.05$) difference for nepafenac suspension relative to placebo

Safety:

- 7 treatment related AEs (TR-AEs) were reported for patients in nepafenac 0.03% group (ocular hyperemia and ocular pruritis, 2.9% incidence for each)
- 5 treatment related AEs were reported for patients in nepafenac 0.1%, incidence 1.4%
- 4 treatment related AEs were reported in nepafenac 0.3% group, most frequent event ocular hyperemia, incidence 2.9%
- 16 treatment related AEs were reported in placebo group; most frequent was ocular pruritis (4.2%)
- No deaths or treatment related serious AEs occurred and no patients discontinued the study due to serious AEs.
- 3 patients D/Cd treatment for TR-AE: 1 patient 0.1% (conjunctivitis) and 2 patients placebo (iritis and ocular pain and photophobia)
- 6 patients D/Cd study for non-serious AE of mild to moderate intensity not related to study drug

Conclusions

Nepafenac suspension 0.03%, 0.1%, and 0.3% administered 1 drop QID appeared to be effective, well tolerated, and safe for the treatment and prevention of pain and inflammation associated with cataract surgery and IOL implantation.

Critique

Strengths

Used intention to treat analysis and showed distribution of patients excluded from analysis.

Limitations

Not a published, peer reviewed trial.

<table>
<tr><td>Citation</td><td>NEVANAC (nepafenac ophthalmic suspension 0.1%) Managed Care Dossier. Data on file. C-97-30.</td></tr>
<tr><td>Study Goals</td><td>To evaluate the efficacy of nepafenac suspension (0.003%, 0.01%, 0.03%, and 0.1%) for the treatment of inflammation in patients requiring cataract surgery.</td></tr>
<tr><td>Methods</td><td>Study Design
Design: multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose response study
Treatment groups: (n=197)
➢ Nepafenac 0.003% (n=40)
➢ Nepafenac 0.01% (n=41)
➢ Nepafenac 0.03% (n=37)
➢ Nepafenac 0.1% (n=40)
➢ Vehicle/placebo (n=39)
All treatments were given as 1 drop in the affected eye QID beginning 1 day after surgery and continuing for 14 days postoperatively (total of 14 days)
Length of study: 14 days
Efficacy measures used: (measured at day 1,4,8,and 15 post operatively)
➢ Primary: Mean change from baseline in aqueous cell score, Mean change from baseline in aqueous flare score, Mean change from baseline in cells + flare score
➢ Secondary: Percent cures (cells + flare score = 0) at day 15, Percent treatment failures (cells + flare score ≥ baseline score)
Data Analysis
➢ Intention to treat analysis was preformed.
➢ P< 0.05 was considered to be statistically significant</td></tr>
<tr><td>Criteria</td><td>Inclusion criteria
➢ Men of women of any gender ≥ 18 years of age
➢ Individuals who had a cataract and were expected to undergo cataract extraction with the implantation of a posterior chamber intraocular lens
➢ Clinically significant inflammation (cells + flare score ≥ 4 and a flare score ≥ 2 units) on Day 1 postsurgically
Exclusion criteria
➢ Surgical complications
➢ Previous cataract extraction or IOL implantation
➢ Nonfunctional eye
➢ History of chronic or recurrent inflammatory eye disease
➢ Hypersensitivity to NSAIDs or any component of study medication
➢ Topical ocular or systemic corticosteroids w/in 30 days, or NSAIDs w/in 14 days</td></tr>
<tr><td>Results</td><td>Data analysis (all values reported for ITT values for study endpoint, postop. day 15)
<table>
<tr><th>Efficacy Parameter</th><th>NEP 0.003% QID (n=40)</th><th>NEP 0.01% QID (n=41)</th><th>NEP 0.03% QID (n=37)</th><th>NEP suspension 0.1% QID (n=40)</th><th>Placebo (n=39)</th></tr>
<tr><td>Mean Cells Score change from baseline</td><td>-1.45*</td><td>-1.45*</td><td>-1.43*</td><td>-1.35*</td><td>-0.62</td></tr>
<tr><td>Mean Flare Score change from baseline</td><td>-1.53*</td><td>-1.55*</td><td>-1.59*</td><td>-1.68*</td><td>-0.56</td></tr>
<tr><td>Mean Cells + Flare score change from baseline</td><td>-2.98*</td><td>-3.00*</td><td>-3.03*</td><td>-3.03*</td><td>-1.18</td></tr>
<tr><td>% Cures</td><td>27.5%*</td><td>17.5%</td><td>32.4%</td><td>15%</td><td>7.7%</td></tr>
<tr><td>% Treatment failures</td><td>35%</td><td>37.5%</td><td>29.7%*</td><td>32.5%*</td><td>56.4%</td></tr>
</table>
* indicates statistically significant (p<0.05) difference for nepafenac suspension relative to placebo
Safety:
Overall AEs were nonserious, mild or moderate in intensity, usually resolved with or without treatment, and generally did not cause discontinuation from the study.
➢ 2 TR-AEs (foreign body sensation and ocular pain) were reported in patients receiving the 0.003% nepafenac (incidence of 2.5%)
➢ No TR-AEs were reported in the 0.01% treatment group.
➢ 2 TR-AEs (ocular discharge and tearing) were reported for patients in the nepafenac 0.03% group (2.7% incidence)
➢ 3 TR-AEs (iritis, lid margin crusting, and tearing) were reported in the nepafenac 0.1% (2.5% incidence)</td></tr>
</table>

	➢ 8 TR-AEs were reported in the placebo group No deaths or treatment-related serious AEs occurred during the study and no patients in any of the treatment groups D/Cd the study due to serious adverse events.
Conclusions	Nepafenac suspension 0.003%, 0.01%, and 0.03%, and 0.1% administered 1 drop QID appeared to be effective, well tolerated, and safe for the treatment and prevention of pain and inflammation associated with cataract surgery and IOL implantation.
Critique	**Strengths** Used intention to treat analysis and showed distribution of patients excluded from analysis. **Limitations** Not a peer reviewed, published clinical trial.

Citation	NEVANAC (nepafenac ophthalmic suspension 0.1%) Managed Care Dossier. *Data on file*. **C-95-91.**
Study Goals	To compare the safety and tolerability of nepafenac ophthalmic suspension 0.1% and 0.3% with diclofenac ophthalmic solution 0.1% (VOLTAREN OPHTHALMIC) and placebo/vehicle in healthy adults with a normal comprehensive ophthalmic evaluation.
Methods	**Study Design** ***Design:*** single-center, randomized, double-blind, placebo-controlled, four- period crossover study ***Treatment groups:*** (n=24) ➢ Nepafenac 0.1% ➢ Nepafenac 0.3% ➢ Diclofenac solution 0.1% ➢ Vehicle/placebo (n=72) All treatments were given as 1 drop in a single eye with at least a 24-hour washout between treatments ***Length of study:*** unknown ***Safety and Tolerability endpoints:*** Ocular discomfort composite score Membrane discomfort composite score Visual clarity and burning profiles **Data Analysis:** unknown
Criteria	**Inclusion criteria** ➢ Healthy adults ➢ Corrected vision better than 20/50 in each eye **Exclusion criteria** ➢ Acute or chronic pathological ophthalmic condition ➢ Use of routine (OTC or prescription) ocular medications
Results	**Safety:** Nepafenac 0.1% and 0.3% produced significantly less ocular discomfort than diclofenac 0.1% solution Nepafenac 0.1% and 0.3% produced significantly less severe ocular burning profiles than diclofenac 0.1%.
Conclusions	Nepafenac ophthalmic suspension 0.1% and 0.3% appeared to provide significantly less ocular discomfort and less severe ocular burning compared to diclofenac solution 0.1%.
Critique	**Strengths** ➢ Used intention to treat analysis and showed distribution of patients excluded from analysis. **Limitations** ➢ There was no actual clinical trial and information in dossier contained no specific information, only an overview. ➢ This was done in healthy patients, no data on patients undergoing cataract surgery.