Pharmacokinetics of a Hydrogel-based Nepafenac Intracanalicular Insert in Canines

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Disclosures

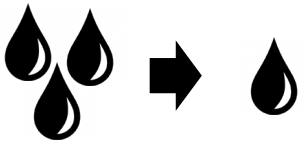
- All authors are employees of Ocular Therapeutix, Inc.
- This study was funded by Ocular Therapeutix, Inc.
- The presentation discusses an investigational product and its efficacy and safety profile has not been established and it has not been approved by the FDA

Background

- Topical NSAIDs are often prescribed to reduce ocular pain and modulate inflammation but may be limited by their reliance on patient self-dosing[1]
- Poor patient adherence to the prescribed treatment regimen can result in subtherapeutic drug levels and compromise patient outcomes[2]
- Multiple solutions exist to overcome adherence issues however, the dosing responsibility still rests with the patient

Reminder strategies[3]

Dosing aides[4]



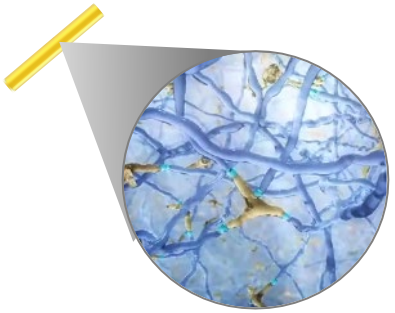
Simplifying dosing regimens[5,6]

Avoidance of preservatives[7]

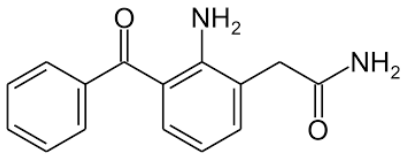
- Sustained–release drug delivery options offers current and future opportunity to reduce or eliminate nonadherence **by shifting the dosing responsibility from the patient to the provider**

References: **1**. Matossian C, Nattis AS, Nijm LM, et al. Real-World Time Savings on Patient Education and Call-Backs Related to Post-Cataract Therapy Using an Intracanalicular Dexamethasone Insert. Presented at the American Society of Cataract and Refractive Surgeons Annual Meeting. July 23-27, 2021. Las Vegas, NV. **2.** Feng A, O'Neill J, Holt M, et al. *Clin Ophthalmol*. 2016;10:1505-1511. **3.** Cook PF, et al. *Psychol Health* 2017;32:145-65. **4.** Rivers PH. *Drugs Aging*. 1992;2:103-11. **5.** Budenz DL. *Ophthalmology*. 2009;116:S43-7. **6.** Tsai JC. Et al. *Ophthalmology*. 2009;116:S30-6. **7.** Goldstein MH, et al. Eye (Lond). 2022;36(2):361-368.

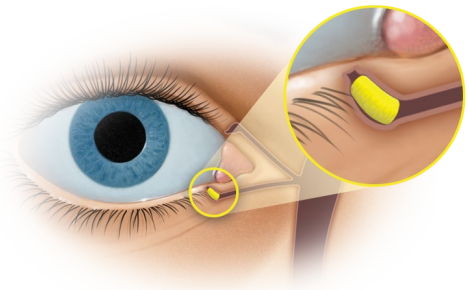
Nepafenac Intracanalicular Insert



Polyethylene Glycol Hydrogel
(Inactive Delivery Platform)



Nepafenac
(Active Ingredient)



Nepafenac
Intracanalicular Insert

- Contains nepafenac (active ingredient) in a polyethylene glycol (PEG) hydrogel (inactive delivery platform)
- Single insert designed to release nepafenac to the ocular surface in a sustained fashion as an alternative to traditional topical eye drops
- Fully biodegradable insert; no need for removal
- Preservative-free
- Conjugated with fluorescein for visualization purposes

Study Objective and Design

Objective

- To evaluate the pharmacokinetics of nepafenac delivered from a biodegradable hydrogel intracanalicular insert in a canine model

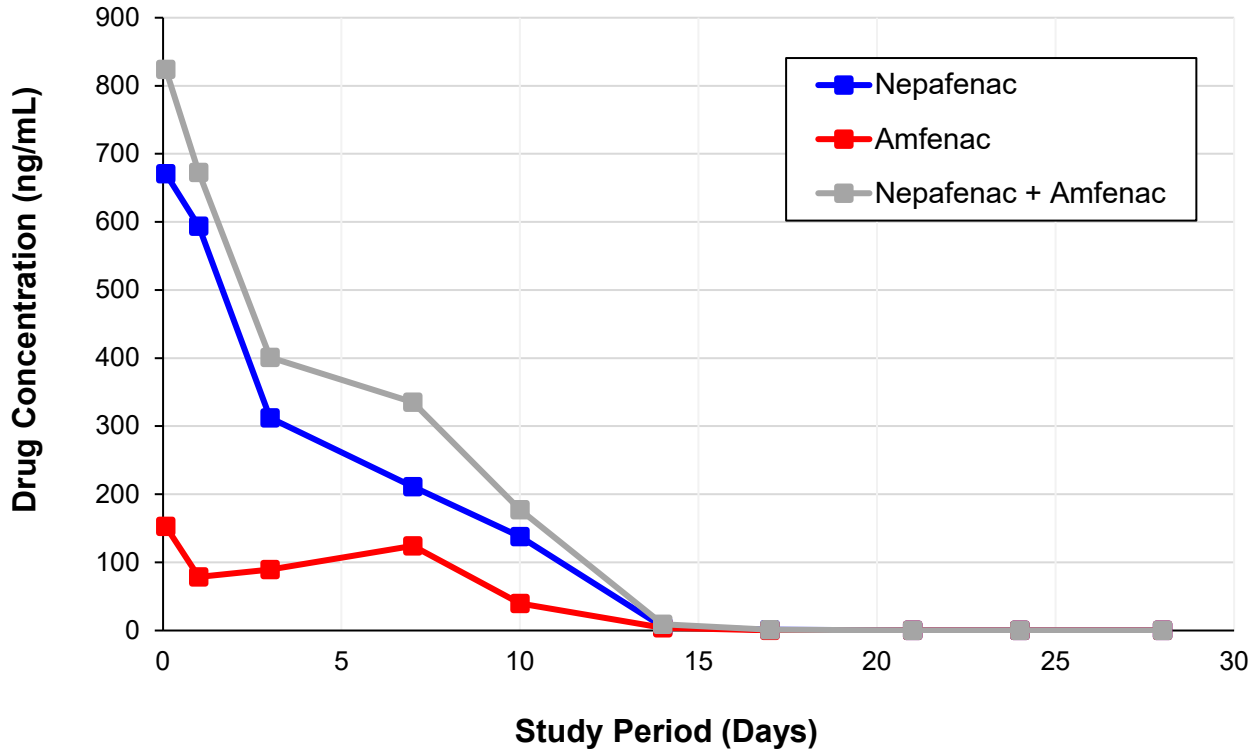
Study Design

- Inserts were placed bilaterally into the inferior canaliculus of 20 beagle dogs on Day 0.
- Presence of the insert in the canaliculus was confirmed visually
- Tear fluid and aqueous humor samples were collected and measured for nepafenac (prodrug) & amfenac (active metabolite) concentrations

Assessments	Timepoints (Post-Insertion)	Method
Tear Fluid Collection (using Schirmer Tear Test Strips, n=10 samples/timepoint)	2 hours and 1, 3, 7, 10, 14, 17, 21, 24, and 28 days	Liquid Chromatography with Tandem Mass Spectrometry
Aqueous Humor Collection (0.1 mL, n=6 samples/timepoint)	7, 14, 21, and 28 days	Liquid Chromatography with Tandem Mass Spectrometry

Insert Demonstrated Rapid and Sustained-delivery of Nepafenac to the Tear Fluid Over 10-14 Days

Figure 2. Nepafenac and Amfenac Tear Fluid Concentrations Following Administration of Low Dose Nepafenac Intracanalicular Insert



Tear Fluid Pharmacokinetics

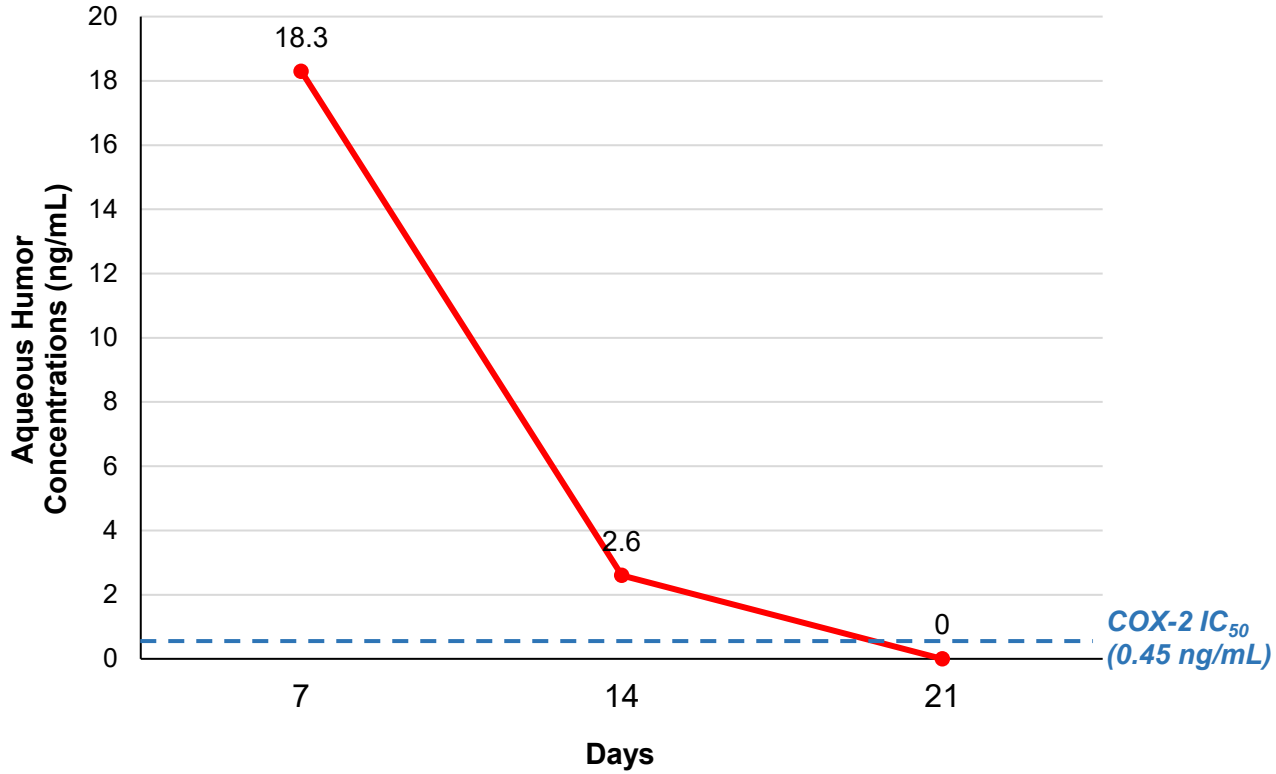
- Maximum mean concentration of nepafenac (671 ng/mL) and amfenac (153 ng/mL) were measured at 2 hours post-insertion
- Tear fluid drug levels gradually tapered over time and were cleared from the tear fluid by 10-14 days
- Both nepafenac and amfenac were found in the tear fluid in an 85:15 ratio, however, only amfenac was detected in aqueous humor

Inserts Achieved Therapeutic Levels of Active Metabolite, Amfenac, in the Aqueous Humor

Aqueous Humor Pharmacokinetics

- Amfenac concentration in the aqueous humor was greatest on Day 7 at 18.3 ng/mL
- Levels of amfenac in the aqueous humor on Day 7 were 41-fold above the inhibitory concentration of cyclooxygenase-2 (COX-2 IC_{50} = 0.45 ng/mL) suggesting a potential therapeutic effect at these concentrations

Figure 3. Amfenac Concentrations in the Aqueous Humor Following Administration of a Low Dose Nepafenac Intracanalicular Insert



Conclusions

- In the current study, a hydrogel-based intracanalicular insert containing a low dose of nepafenac **quickly released drug at therapeutic levels to the ocular surface and continued for 10-14 days**
- **Levels of amfenac in the aqueous humor suggest a potential therapeutic effect** at the concentrations measured in this study
- Ocular pharmacokinetic studies of inserts with higher drug doses are needed to further characterize the release profile of nepafenac
- Sustained-release delivery of nepafenac offers a potential new modality for preservative-free drug delivery that can overcome limitations of existing topical therapies