# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 210821Orig1s000

## MULTI-DISCIPLINE REVIEW

**Summary Review**
**Office Director**
**Cross Discipline Team Leader Review**
**Clinical Review**
**Non-Clinical Review**
**Statistical Review**
**Clinical Pharmacology Review**

# Clinical Review, Division Director Summary Review and Cross Discipline Team Leader Review of NDA 210821

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 210-821 |
| Amendment Submit Date(s) | February 25, 2019, March 5, 2019 |
| Division/Office | Division of Transplant and Ophthalmology/Office of New Drugs |
| Review Completion Date | March 12, 2019 |
| Established Name | Tetracaine hydrochloride ophthalmic solution, USP, 0.5% |
| Pharmacologic Class | Ophthalmic anesthetic |
| Applicant | Bausch Health Ireland Limited |
| Dosing Regimen | One drop topically applied to the eye as needed |
| Applicant Proposed Indication(s)/Population(s) | For procedures requiring a rapid short-acting topical ophthalmic anesthetic |
| Regulatory Action | Approval |

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# Review Team

| | |
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| Nonclinical Reviewer | Erin Ruhland |
| Nonclinical Team Leader | Lori Kotch |
| Clinical Reviewer | Wiley A. Chambers |
| Clinical Team Leader | William M. Boyd |
| Statistical Reviewer | Abel Eshete |
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| Environmental Assessment (EA) | Shrikant Pagay | Balajee Shanmugam |

# 1 Executive Summary

## 1.1. Application Summary Action

Tetracaine hydrochloride ophthalmic solution is one of several topical anesthetic products marketed for decades in the United States without an approved new drug application. Tetracaine is also known as amethocaine and pontocaine. The drug product facility was initially found to not be in compliance with current good manufacturing practices, but this deficiency has been corrected and the application can now be approved.

## 1.2. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Temporary anesthesia of the cornea and conjunctiva allow ophthalmic procedures to be performed because the patient will not have a touch or pain reflex and can remain still during the procedure. The localized anesthesia limits potential injuries to the local area anesthetized. The temporary duration limits long term risks.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • The cornea and conjunctiva have numerous touch and pain receptors. There are multiple ophthalmic procedures which require a patient to hold still in order to be completed. Patients will not hold still if their eye hurts. | Corneal and conjunctival anesthesia are required for patients to be able to hold still during ophthalmic procedures. |
| Current Treatment Options | • Tetracaine ophthalmic solution, lidocaine ophthalmic solution and proparacaine ophthalmic solution will provide corneal and conjunctival anesthesia. | Topical corneal and conjunctival anesthetics have been used for decades to provide corneal anesthesia. |
| Benefit | • The intended procedure can be completed. | Anesthesia interferes with the perception of pain and touch, minimizing pain during the procedure. |
| Risk and Risk Management | • Corneal and conjunctival anesthesia inhibit self defense reflexes and healing mechanisms of the cornea and conjunctiva. | The short-term duration and localized area of effect limit potential injuries. |

### 1.3. Patient Experience Data

This product causes topical, local anesthesia resulting in a temporary (20 minutes) absence of sensation at the site of application.

Patient Experience Data Relevant to this Application (check all that apply)

| | | | | |
|---|---|---|---|---|
| √ | The patient experience data that was submitted as part of the application, include: | | | |
| | √ | Clinical outcome assessment (COA) data, such as | | |
| | | | √ | Patient reported outcome (PRO) |
| | | | □ | Observer reported outcome (ObsRO) |
| | | | √ | Clinician reported outcome (ClinRO) |
| | | | □ | Performance outcome (PerfO) |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | □ | Natural history studies | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | □ | Other: (Please specify) | | |
| □ | Patient experience data that was not submitted in the application, but was considered in this review. | | | |

## 2 Therapeutic Context

### 2.1. Analysis of Condition

Topical anesthesia is desired to effectively perform a number of ophthalmic examinations and procedures. Ideally, the anesthetic agent can be easily applied, will provide effective anesthesia throughout the procedure and has a duration of action that minimizes the risks of patient self-injury after the procedure is complete.

### 2.2. Analysis of Current Treatment Options

| Tradename | Established Name | NDA Number | Indication |
|---|---|---|---|
| Tetracaine | Tetracaine ophthalmic solution, 0.5% | NDA 208-135 | For procedures requiring a rapid and short-acting topical ophthalmic anesthetic |
| Alcaine | Proparacaine ophthalmic solution, 0.5% | ANDA 80-027<br>ANDA 80-027<br>ANDA 40-277<br>ANDA 87-681<br>ANDA 40-074 | For topical anesthesia in ophthalmic practice. |
| Akten | Lidocaine ophthalmic gel, 3.5% | **NDA** 22-221 | For local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures |

### 2.3. Alternative Tetracaine Ophthalmic Products

**COMPOSITION OF THE DRUG PRODUCT:**

| Component | NDA 210182 Amount (% w/v) | NDA 208135 Amount (% w/v) | Function |
|---|---|---|---|
| Tetracaine Hydrochloride | 0.5% | 0.5* | Active |
| Boric Acid | (b) (4) | (b) (4) | (b) (4) |
| Edetate disodium | | | |
| Sodium Acetate (trihydrate) | | | |
| Sodium chloride | | | |
| Potassium chloride | | | |
| Chlorobutanol | 0.4% | | Antimicrobial Preservative |
| Hydrochloric acid and/or sodium hydroxide | Target pH | | pH Adjustor |
| Acetic acid and/or sodium acetate | | Target pH of 4.5 | pH Adjustor |
| Water for Injection | qs to 100% | qs to 100% | Vehicle |

## 3 Regulatory Background

Tetracaine Hydrochloride is a topical anesthetic used since at least the 1930s. While several different formulations have been successfully used to anesthetize the eye, the formulation which is the subject of this NDA, Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% was originally developed by Pharmafair, Inc. in Happauge, NY. Bausch & Lomb (B&L) purchased the product and transferred it, as is, to the Tampa, Florida manufacturing facility in 1992. The product formulation and specifications were maintained throughout the technology transfer, and there have been few changes since 1992. In 1997, a (b) (4) preservative (chlorobutanol) was added to accoun (b) (4) the active pharmaceutical ingredient in the formulation was maintained to utilize the vast amount of historical data available to support

this NDA. The 0.5% label claim remains the same to comply with the historically labeled product. In addition, alternate drug substance suppliers were validated in 1994 and in 2005. The current drug substance manufacturer (b) (4) has been the sole source of drug substance since 2005.

Tetracaine has been reported to be self-preserving in the literature. The effectiveness of the preservative (chlorobutanol) has been investigated at approximate concentrations of 0%, 5%, 10%, 20%, 80%, 100% and 120% of label claim (0.4%). The formulation was found to meet all requirements of antimicrobial effectiveness testing, USP <51> at each of the above referenced concentrations. Passing USP <51> with a chlorobutanol concentration of zero is equivalent to a self-preserving solution. While the drug product is sufficiently self-preserving to pass the USP test requirement, testing of formulations with 5% of the chlorobutanol label claim or higher demonstrated a higher kill effectiveness.

## 4 Significant Issues from Other Review Disciplines

### Office of Scientific Investigations (OSI)

The clinical portion of the application is based on published literature studies. Based on the large number of consistent study results and the widespread use of this product in clinical practice, no inspections were requested from OSI.

## 5 Nonclinical Pharmacology/Toxicology

The applicant is relying on the 45-year marketing history of tetracaine and has not conducted any non-clinical studies to support the application. As a short acting, topical anesthetic with negligible systemic absorption, there are no carcinogenic, teratogenic or systemic toxicity questions that need to be addressed by nonclinical studies. Local toxicity issues and pharmacodynamics studies are better addressed by the human clinical studies available in the literature than by non-clinical studies.

## 6 Clinical Pharmacology/Biopharmaceutics

The applicant did not conduct any clinical pharmacology related studies and requested the waiver of evidence of in vivo bioavailability or bioequivalence. In accordance with the 21 CFR §320.22(e), the Biopharmaceutics reviewer recommended granting the waiver of evidence of in vivo bioavailability or bioequivalence to this NDA on the basis of the compatibility with the protection of public health due to its long history of clinical use. I concur with the waiver.

## 7 Summary of Office of Pharmaceutical Quality

Drug substance, drug product, biopharmaceutics, manufacturing process and quality micro reviewers have recommended approval of NDA 210821 as documented in IQA #1 dated 11/2/2018. The drug product manufacturing facility, Bausch & Lomb at Tampa, FL (FEI:

1000113778) is classified as NAI based on the recent inspection ending Jan 30, 2019. The Office of Process and Facilities has issued an overall acceptable recommendation for all the facilities on Feb 28, 2019. Therefore, NDA 210821 is recommended for APPROVAL from the Product Quality perspective. Labeling recommendations from the Product Quality perspective were provided to the OND PM for consideration during the original NDA review cycle.

Release and shelf life specifications for Tetracaine Hydrochloride Ophthalmic

| Test | Procedure | Acceptance Criteria | |
|---|---|---|---|
| | | Release | Shelf Life (Stability) |
| Description | Visual (b) (4) | Colorless to slightly yellow solution. | Colorless to slightly yellow solution. |
| (b) (4) | | | |

# 8 Clinical Pharmacology

The drug product is topically applied to the cornea. There is little or no measurable systemic absorption.

# 9 Sources of Clinical Data and Review Strategy

Clinical Studies

All literature reports submitted by the Applicant were reviewed to determine if the design and results of the study supported the use of tetracaine 0.5% as a topical ophthalmic anesthetic. Studies in which the tetracaine ophthalmic solution is a 0.5% concentration, a formulation consistent with the one proposed in this NDA and either having an unidentified source or identified as being sourced by Valent, Bausch & Lomb or Pharmafair are included in the first table below and used to support this application. Studies in which the tetracaine ophthalmic solution is identified as specifically being sourced by a company other than Valent, Bausch & Lomb or Pharmafair have been identified and included in a second table below because they are used to support this application.

| Study | Design | Objective | Subjects | Treatment | B&L Product |
|---|---|---|---|---|---|
| Barequet 1999 | Randomized | To compare the efficacy of lidocaine with tetracaine for topical anesthesia in clear corneal cataract surgery | 25 | Single application of lidocaine 2% gel or 1 drop of 0.5% tetracaine | Unknown |
| Blaha 2011 | Prospective, masked, randomized | To compare the effectiveness of four different anesthetic methods for intravitreal injection | 24 | Proparacaine 0.5%<br>Tetracaine 0.5%<br>Lidocaine 4% pledget<br>Lidocaine 2% | Yes (Bausch and Lomb) |
| Carden 1998 | Randomized, controlled, observer masked | To test the effect of amethocaine on reducing postoperative pain, vomiting, and length of stay in children having strabismus repair | 62 (6 months–15 years) | 2 drops of 0.5% amethocaine*, subconjunctival bupivacaine 0.5%, or placebo (saline) | Unknown |
| Kim 2003 | Randomized, double-masked, placebo-controlled | To compare the effect of placebo to intraoperative 0.5% topical amethocaine or 0.5% topical ketorolac on pain control after strabismus surgery in children | 51 (2–7 years) | 2 drops of 0.5% amethocaine*, 0.5% ketorolac, or placebo (saline) at the start and end of strabismus repair surgery | Unknown |
| Nomura 2001 | Prospective, randomized | To evaluate corneal touch sensitivity measured by Cochet-Bonnet anesthesiometer | 17 | Tetracaine 0.5%<br>Lidocaine 4%<br>Bupivacaine 0.75%<br>Tetracaine & Lidocaine<br>Tetracaine & Bupivacaine | Unknown |

| Study | Design | Objective | Subjects | Treatment | B&L Product |
|---|---|---|---|---|---|
| Ogun 2014 | Prospective, randomized | To evaluate the potentiating effect of tetracaine on pupil dilation | 50 | Tetracaine Placebo | Unknown |
| Sabermoghadam 2012 | pilot study | to find a new form of lidocaine to give a sufficient level of anesthesia | 30 | Tetracaine Lidocaine cyclodextrin | Unknown |
| Sanabria 2013 | prospective, randomized, double-masked | to evaluate the efficacy of different anesthetics and topical anti-inflammatory treatment in patients undergoing intravitreal injection (IVI) | 156 | Tetracaine 0.5% +naphazoline Lidocaine 5% | Unknown |
| Shafi 1998 | prospective, randomized, double masked | to evaluate the claim that topical proxymetacaine produces little or no discomfort on instillation by comparing it against topical amethocaine | 53 | Proxymetacaine 0.5% Amethocaine* 0.5% | Unknown |
| Tsoumani 2010 | Randomized, controlled, double- masked | To compare the efficacy of tetracaine and the combination of lidocaine application and instillation of tetracaine as methods of topical anesthesia for cataract surgery | 51 | 0.5 cm lidocaine 2% gel plus 1 drop of 0.5% tetracaine or 1 drop of 0.5% tetracaine 5 min apart × 3 | Unknown |
| Yau 2010 | Randomized, observer masked | To compare anesthetic effectiveness of 3 topical agents for intravitreal injections | 93 | Tetracaine 0.5% Cocaine 4% Tetracaine 0.5% & Lidocaine pledget | Unknown |

* Tetracaine is also known as amethocaine and pontocaine.

Studies not used to assess safety and efficacy:

| Study | Design | Objective | Subjects | Treatment | B&L Product |
|---|---|---|---|---|---|
| Amiel 2007 | Randomized, double-masked | To assess the anesthetic efficacy of tetracaine versus lidocaine in routine cataract extraction | 100 | 1-inch ribbon of lidocaine 2% jelly or 1 drop of 0.5% tetracaine | No (Tetravisc) |
| Anninger 2007 | Randomized, double-masked | To test the effect of tetracaine on reducing the intensity and incidence of postoperative pain and emergence agitation after strabismus surgery in children | 88 (1–12 years) | 2 drops of 1% tetracaine before and after surgery with placebo (saline) controls | No (1% solution) |
| Chalam 2009 | randomized, muti-surgeon, controlled study | To compare the clinical efficacy of lidocaine 2% with tetracaine 0.5% for cataract surgery | 122 | lidocaine 2% tetracaine 0.5% | No (Ocusoft) |

| Study | Design | Objective | Subjects | Treatment | B&L Product |
|---|---|---|---|---|---|
| Harman 2000 | Non-masked | To determine whether lidocaine is as efficacious as tetracaine for obtaining ocular anesthesia in cataract surgery | 100 | 0.5-inch strip lidocaine 2% jelly or 2 drops of 0.5% tetracaine 10 min apart | No (Ciba Vision) |
| Moshifar 2014 | Prospective, single-masked, randomized | To evaluate the efficacy of proparacaine and tetracaine for pain control in patients undergoing LASIK and PRK | 256 eyes from 128 patients | Tetracaine 0.5% Proparacaine 0.5% | Tetracaine (Alcon) Proparacaine (B&L) |
| Rifkin 2012 | prospective, randomized | To determine factors associated with patient's comfort during routine in-office intravitreal injection. | 60 | Proparacaine 0.5% TetraVisc Tetracaine 0.5% | Tetravisc (Ocusoft) Tetracaine (Alcon) |
| Watson 1991 | Randomized, observer masked | To assess the effect of topical amethocaine on postoperative analgesia after strabismus surgery in children | 40 (1–12 years) | 2 drops of 1% amethocaine* versus placebo (saline) | No (1% solution) |
| Yu 2003 | Randomized, double-masked, double dummy | To compare the efficacy of lidocaine with amethocaine as the sole anesthetic agent for strabismus surgery | 14 | 1 mL lidocaine 2% gel in one eye and 1 drop of 1% amethocaine* 5 min apart × 3 in fellow eye | No (1% solution) |

* Tetracaine is also known as amethocaine and pontocaine.

The fact that cataract surgery, intraocular pressure measurements or intravitreal injections were able to be performed with tetracaine as the only anesthetic demonstrates the efficacy of tetracaine in producing an anesthetic effect. Each of the published studies describes successful surgery, injections or intraocular pressure measurements. As described in the regulations for adequate and well controlled studies, 21 CFR 314.126, patients could have been their own control (i.e., historical control) because anesthesia would not otherwise be expected to occur. The studies are not sufficiently powered to be able to establish comparative information between tetracaine, proparacaine and lidocaine and therefore it is not possible to establish if any one of these is more effective than any of the other topical ophthalmic anesthetics.

## 10 Safety

The adverse event profile for tetracaine based on the published studies and postmarketing reporting suggest that the most common adverse events are transient events associated with instillation of the drop. These include events such as burning, stinging, discomfort, irritation and pain. Corneal toxicity with damage to the epithelium has also been reported to occur with abuse of anesthetics.

Safety information collected from current marketing
The safety data available for review does not allow for a quantitative determination of the exact incidence of each type of adverse reactions. Pooling of the safety results from the

published reports and postmarketing data cannot be used to provide quantitative safety information.

In the post-marketing database, of the 357 reported reaction events, 182 were eye disorders, 43 of these events were instillation site reactions (erythema, pain, swelling). Of the non-ocular events 55 involved ineffective drug reports.

A summary of postmarketing safety data including spontaneous adverse reaction reports and reports in published literature with a cutoff date of January 16, 2018, is provided below. During the reporting period the company estimated that over 3 million units had been sold in the US.

There were 357 adverse reactions reported in 213 patients. The vast majority of these reports are eye disorders (n=182), 43 events were instillation site reactions (erythema, pain, swelling). Of the non-ocular events 55 involved ineffective drug reports. Of the total adverse reaction reports 189 patients were derived from spontaneous reports and 24 patients from the published literature or clinical studies.

Distribution data for Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% (2013-2016)

| NDC | Product | 2013 Units | 2014 Units | 2015 Units | 2016 Units | Total Units |
|---|---|---|---|---|---|---|
| 24208-0920-64 | Tetracaine Hydrochloride Ophthalmic Solution 0.5%, | (b) (4) | | | | |

Reported Adverse Reactions

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Drug ineffective | 41 | 35 | 6 |
| Instillation site pain | 37 | 36 | 1 |
| Eye irritation | 17 | 17 | 0 |
| Ocular hyperemia | 15 | 15 | 0 |
| Eye pain | 14 | 13 | 1 |
| Medication error | 11 | 11 | 0 |
| Corneal epithelium defect | 10 | 7 | 3 |
| Corneal edema | 10 | 7 | 3 |
| Drug ineffective for unapproved indication | 10 | 10 | 0 |
| Hypersensitivity | 7 | 7 | 0 |
| Iridocyclitis | 7 | 3 | 4 |
| Vision blurred | 7 | 7 | 0 |
| Conjunctival hyperemia | 6 | 4 | 2 |
| Pain | 6 | 2 | 4 |

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Visual impairment | 6 | 6 | 0 |
| Eye infection | 5 | 5 | 0 |
| Mydriasis | 5 | 4 | 1 |
| Punctate keratitis | 5 | 3 | 2 |
| Off label use | 4 | 4 | 0 |
| Prescription drug used without a prescription | 4 | 0 | 4 |
| Accidental Exposure to Product | 3 | 3 | 0 |
| Corneal disorder | 3 | 2 | 1 |
| Dermatitis allergic | 3 | 3 | 0 |
| Discomfort | 3 | 2 | 1 |
| Drug interaction | 3 | 3 | 0 |
| Eyelid edema | 3 | 3 | 0 |
| Photophobia | 3 | 3 | 0 |
| Anaphylactic reactions | 2 | 2 | 0 |
| Anaphylactic shock | 2 | 2 | 0 |
| Corneal abrasion | 2 | 1 | 1 |
| Corneal defect | 2 | 2 | 0 |
| Corneal opacity | 2 | 2 | 0 |
| Corneal pigmentation | 2 | 2 | 0 |
| Dizziness | 2 | 2 | 0 |
| Drug effect decreased | 2 | 2 | 0 |
| Eczema | 2 | 2 | 0 |
| Expired product administered | 2 | 2 | 0 |
| Eye swelling | 2 | 2 | 0 |
| Injection site pain | 2 | 2 | 0 |
| Lacrimation increased | 2 | 2 | 0 |
| No adverse event | 2 | 2 | 0 |
| Ocular discomfort | 2 | 2 | 0 |
| Sinus arrhythmia | 2 | 2 | 0 |
| Visual acuity reduced | 2 | 2 | 0 |
| Asthenia | 1 | 1 | 0 |
| Blindness | 1 | 1 | 0 |

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Blood pressure increased | 1 | 1 | 0 |
| Bradycardia | 1 | 1 | 0 |
| Burning sensation mucosal | 1 | 1 | 0 |
| Chemical burns of eyes | 1 | 0 | 1 |
| Circulatory collapse | 1 | 1 | 0 |
| Corneal decompensation | 1 | 0 | 1 |
| Corneal infiltrates | 1 | 0 | 1 |
| Corneal neovascularization | 1 | 1 | 0 |
| Corneal perforation | 1 | 1 | 0 |
| Corneal scar | 1 | 0 | 1 |
| Corneal thinning | 1 | 1 | 0 |
| Dermatitis contact | 1 | 1 | 0 |
| Diplopia | 1 | 1 | 0 |
| Drug effect incomplete | 1 | 1 | 0 |
| Drug effect prolonged | 1 | 1 | 0 |
| Drug screen positive | 1 | 1 | 0 |
| Dysgeusia | 1 | 1 | 0 |
| Dyspnea | 1 | 1 | 0 |
| Dystasis | 1 | 1 | 0 |
| Eczema weeping | 1 | 1 | 0 |
| Emotional distress | 1 | 1 | 0 |
| Endophthalmitis | 1 | 1 | 0 |
| Erythema | 1 | 1 | 0 |
| Eye disorder | 1 | 0 | 1 |
| Eye excision | 1 | 1 | 0 |
| Eye inflammation | 1 | 1 | 0 |
| Eye injury | 1 | 1 | 0 |
| Eyelid irritation | 1 | 1 | 0 |
| Fibrosis | 1 | 1 | 0 |
| Fluid retention | 1 | 1 | 0 |
| Foreign body in gastrointestinal tract | 1 | 1 | 0 |
| Foreign body sensation in eyes | 1 | 1 | 0 |

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Headache | 1 | 1 | 0 |
| Heart rate decreased | 1 | 1 | 0 |
| Hot flush | 1 | 1 | 0 |
| Hyperplasis | 1 | 1 | 0 |
| Hyperthermia malignant | 1 | 1 | 0 |
| Hypotension | 1 | 1 | 0 |
| Injection site erythema | 1 | 1 | 0 |
| Injection site pruritus | 1 | 1 | 0 |
| Injection site swelling | 1 | 1 | 0 |
| Iridocele | 1 | 1 | 0 |
| Laboratory test abnormal | 1 | 1 | 0 |
| Leukocytosis | 1 | 1 | 0 |
| Loss of consciousness | 1 | 1 | 0 |
| Malaise | 1 | 1 | 0 |
| Miosis | 1 | 1 | 0 |
| Mucous membrane disorder | 1 | 1 | 0 |
| Nausea | 1 | 1 | 0 |
| Neovascularization | 1 | 0 | 1 |
| Oropharangeal swelling | 1 | 1 | 0 |
| Palpitations | 1 | 1 | 0 |
| Periorbital edema | 1 | 1 | 0 |
| Pharyngeal edema | 1 | 1 | 0 |
| Product quality issue | 1 | 1 | 0 |
| Product use in unapproved indication | 1 | 1 | 0 |
| Pruritus | 1 | 1 | 0 |
| Rash generalized | 1 | 1 | 0 |
| Retching | 1 | 1 | 0 |
| Skin discoloration | 1 | 1 | 0 |
| Skin disorder | 1 | 1 | 0 |
| Skin exfoliation | 1 | 1 | 0 |
| Skin fissures | 1 | 1 | 0 |
| Skin test positive | 1 | 1 | 0 |

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Swelling | 1 | 1 | 0 |
| Swelling face | 1 | 1 | 0 |
| Swollen tongue | 1 | 1 | 0 |
| Syncope | 1 | 1 | 0 |
| Ulcerative keratitis | 1 | 1 | 0 |
| Under dose | 1 | 1 | 0 |
| Unresponsive to stimuli | 1 | 1 | 0 |
| Urticaria | 1 | 1 | 0 |
| Wheezing | 1 | 1 | 0 |

| | | | |
|---|---|---|---|
| Total AEs | 357 | 317 | 40 |
| Total Patients | 213 | 189 | 24 |

Financial Disclosure
Not applicable. All studies were literature based and did not identify the source of financial support for the study.

## 11 Advisory Committee Meeting

There were no issues identified that were believed to benefit from an advisory committee presentation and/or discussion. No advisory committee meeting was held.

## 12 Pediatrics

Published clinical studies included pediatric patients from birth through 17 years of age. There are no differences between pediatric patients and adult patients in anesthetizing the eye with tetracaine ophthalmic solution.

## 13 Risk Evaluation and Mitigation Strategies (REMS)

Based on the topical, local administration, short duration, negligible systemic absorption of this product and well recognized 70+ years of clinical use, no safety issues requiring mitigation strategies are warranted.

## 14 Postmarketing Requirements and Commitment

None.

# 15 Labeling Recommendations

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% safely and effectively. See full prescribing information for Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%.**

**Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%, for topical ophthalmic use**

**Initial U.S. Approval: 1965**

**INDICATIONS AND USAGE**

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%, is an ester local anesthetic indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic. (1)

**DOSAGE AND ADMINISTRATION**

One drop topically in the eye(s) as needed. (2)

**DOSAGE FORMS AND STRENGTHS**

Sterile, preserved, ophthalmic solution containing 0.5% tetracaine hydrochloride. (3)

**CONTRAINDICATIONS**

Tetracaine Hydrochloride Ophthalmic Solution, 0.5% should not be used in patients with a history of hypersensitivity to any component of this preparation. (4)

**WARNINGS AND PRECAUTIONS**

- Do not use intracamerally since use may damage corneal endothelial cells. (5.1)
- Prolonged use or abuse may lead to corneal epithelial toxicity and may manifest as epithelial defects which may progress to permanent corneal damage. (5.2)
- Patients should not touch the eye for at least 10-20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye. (5.3)

**ADVERSE REACTIONS**

Ocular adverse events: transient stinging, burning, conjunctival redness, eye irritation, eye pain, ocular discomfort. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb, a Division of Valeant Pharmaceuticals North America LLC,. at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 3/2019**

**FULL PRESCRIBING INFORMATION: CONTENTS***



***Sections or subsections omitted from the full prescribing information are not listed.**

# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic.

## 2 DOSAGE AND ADMINISTRATION

One drop topically in the eye(s) as needed.

## 3 DOSAGE FORMS AND STRENGTHS

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is a clear, colorless, ophthalmic solution containing 0.5% w/v tetracaine hydrochloride equivalent to tetracaine 0.44% w/v.

## 4 CONTRAINDICATIONS

Tetracaine Hydrochloride Ophthalmic Solution, USP, 0.5% should not be used in patients with a history of hypersensitivity to any component of this preparation.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Corneal Injury with Intracameral Use

Not for injection or intraocular use. Do not use intracamerally because use of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% may lead to damage of the corneal endothelial cells.

### 5.2 Corneal Toxicity

Prolonged use or abuse may lead to corneal epithelial toxicity and may manifest as epithelial defects which may progress to permanent corneal damage.

### 5.3 Corneal Injury due to Insensitivity

Patients should not touch the eye for at least 10-20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

## 6 ADVERSE REACTIONS

The following serious ocular adverse reactions are described elsewhere in the labeling:

- Corneal Injury with Intracameral Use [See Warnings and Precautions (5.1)]
- Corneal Toxicity [See Warnings and Precautions (5.2)]
- Corneal Injury due to Insensitivity [See Warnings and Precautions (5.3)]

The following adverse reactions have been identified following use of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliable estimate their frequency or establish a causal relationship to drug exposure.

**Ocular Adverse Reactions**
Transient stinging, burning, and conjunctival redness, eye irritation, eye pain, ocular discomfort.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary
There are no adequate and well-controlled studies with Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% in pregnant women. Animal developmental and reproductive toxicity studies with tetracaine hydrochloride have not been reported in the published literature.

### 8.2 Lactation

Risk Summary
There are no data to assess whether Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is excreted in human milk or to assess its effects on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% and any potential adverse effects on the breastfed child from Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%.

### 8.3 Females and Males of Reproductive Potential
No human data on the effect of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% on fertility are available.

### 8.4 Pediatric Use
Safety of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% in the pediatric population has been demonstrated in clinical trials. Efficacy of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% for use in pediatric patients has been extrapolated from adequate and well controlled clinical trials in the adult population.

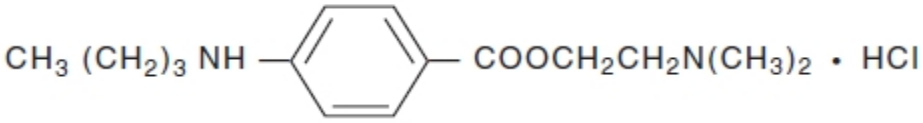
### 8.5 Geriatric Use
No overall differences in safety or effectiveness of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% have been observed between elderly and younger patients.

## 10 OVERDOSAGE
Prolonged use of a topical ocular anesthetic including Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% may produce permanent corneal opacification and ulceration with accompanying visual loss.

## 11 DESCRIPTION
Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is a sterile, clear, colorless, topical local anesthetic for ophthalmic use containing tetracaine hydrochloride as the active pharmaceutical ingredient.

Tetracaine hydrochloride is chemically designated as benzoic acid, 4-(butylamino)-,

2-(dimethylamino) ethyl ester, monohydrochloride. Its chemical formula is $C_{15}H_{24}N_2O_2 \cdot HCl$ and it is represented by the chemical structure:




Tetracaine hydrochloride is a fine, white, crystalline, odorless powder with a molecular weight of 300.82

**Active ingredient**: tetracaine hydrochloride 0.5% w/v (equivalent to 0.44% w/v tetracaine)
**Preservative**: chlorobutanol 0.4%
**Inactive ingredients**: boric acid, potassium chloride, edetate disodium, water for injection USP. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH (3.7 – 6.0)

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Tetracaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses thereby affecting local anesthesia.

### 12.3 Pharmacokinetics

The systemic exposure to tetracaine following topical ocular administration of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% has not been studied. Tetracaine hydrochloride is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess the genotoxicity of tetracaine hydrochloride have not been reported in the published literature. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of tetracaine hydrochloride. Animal studies to assess the effects of tetracaine hydrochloride on fertility have not been reported in the published literature.

## 14 CLINICAL STUDIES

Topical administration of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% results in localized temporary anesthesia. The maximum effect is achieved within 10–20 seconds after instillation, with efficacy lasting 10–20 minutes. Duration of effect can be extended with repeated dosing. [See Warnings and Precautions (5.2) and Overdosage (10)].

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is supplied as a sterile, aqueous, topical ophthalmic solution with a fill volume of 15 mL in a 15 mL low-density polyethylene plastic dropper bottle with a low-density polyethylene dropper tip and white polypropylene cap.

**NDC 42702-170-15**

After opening, this product can be used until the expiration date stamped on the bottle.

**Storage**: Store at 15°C to 25°C (59°F to 77°F). Protect from light. Do not use if solution contains crystals, cloudy, or discolored.

## 17 PATIENT COUNSELING INFORMATION

**Eye Care Precaution**
Do not touch the dropper tip to any surface as this may contaminate the solution.

Advise patients that, due to the effect of the anesthetic, their eyes will be insensitive for up to 20 minutes and that care should be taken to avoid accidental injuries.

Manufactured for:
Paragon BioTeck, Inc.
4640 SW Macadam Ave, Ste 80
Portland, OR 97239

Manufactured and Distributed by:
Bausch & Lomb
8500 Hidden River Pkwy
Tampa, FL 33637
Revised: March 2019

Container Label:

**Each mL Contains:**

**Active:** Tetracaine Hydrochloride, 5 mg (0.5%).

**Preservative:** Chlorobutanol 0.4%.

**Inactives:** Boric Acid, Potassium Chloride, Edetate Disodium, Water for injection. Sodium Hydroxide and/or Hydrochloric Acid may be added to adjust pH (3.7-6.0).

**Manufactured for:**
Paragon BioTeck, Inc.
Portland, OR 97239
© Paragon BioTeck, Inc.

**Manufactured by:**
Bausch & Lomb
8500 Hidden River Pkwy
Tampa, FL 33637

**NDC 42702-170-15**

Paragon BioTeck, Inc.

# Tetracaine Hydrochloride Ophthalmic Solution, USP 0.5% (Sterile)

FOR OPHTHALMIC USE.

**Usual Dosage:**
See package insert.

KEEP OUT OF REACH OF CHILDREN.

After opening, this product can be used until the expiration date stamped on the bottle.

**Storage:** Store between 15°-25°C (59°-77°F).

KEEP TIGHTLY CLOSED.

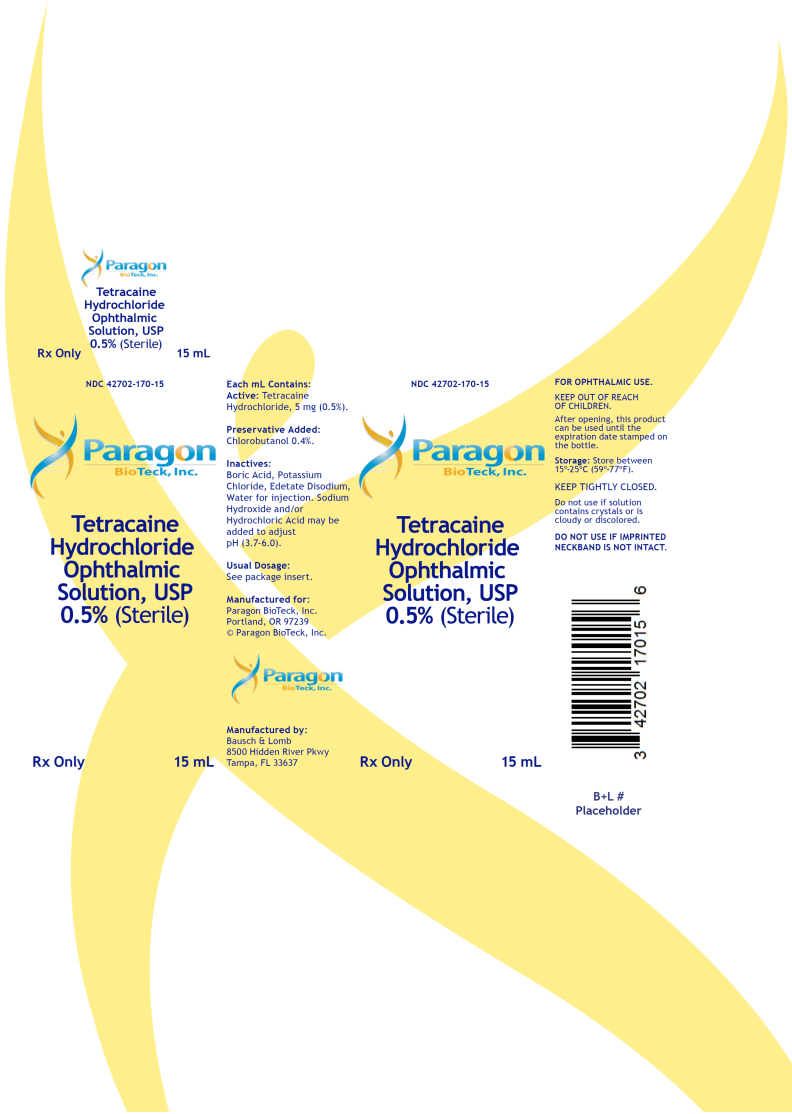
Do not use if solution contains crystals or is cloudy or discolored.

**DO NOT USE IF IMPRINTED NECKBAND IS NOT INTACT.**

(01)00342702170156

**Rx Only** **15 mL**

Carton Label:

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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WILEY A CHAMBERS
03/12/2019 03:28:46 PM

WILLIAM M BOYD
03/12/2019 03:57:49 PM

# Clinical Review, Division Director Summary Review and Cross Discipline Team Leader Review of NDA 210821

| | |
|---|---|
| Application Type | NDA |
| Application Number(s) | 210-821 |
| Priority or Standard | Standard Review |
| Submit Date(s) | February 20, 2018 |
| Received Date(s) | February 20, 2018 |
| Division/Office | Division of Transplant and Ophthalmology/Office of New Drugs |
| Review Completion Date | November 19, 2018 |
| Established Name | Tetracaine hydrochloride ophthalmic solution, USP, 0.5% |
| (Proposed) Trade Name | N/A |
| Pharmacologic Class | Ophthalmic anesthetic |
| Applicant | Valeant Pharmaceuticals |
| Dosing Regimen | One drop topically applied to the eye as needed |
| Applicant Proposed Indication(s)/Population(s) | For procedures requiring a rapid short-acting topical ophthalmic anesthetic |
| Regulatory Action | Complete Response |

## Table of Contents

# Reviewers of Multi-Disciplinary Review and Evaluation

| | |
|---|---|
| Regulatory Project Manager | Eithu Lwin |
| Nonclinical Reviewer | Aaron Ruhland |
| Nonclinical Team Leader | Lori Kotch |
| Clinical Reviewer | Wiley A. Chambers |
| Clinical Team Leader | William M. Boyd |
| Statistical Reviewer | Abel Eshete |
| Statistical Team Leader | Yan Wang |
| Cross-Disciplinary Team Leader | William Boyd |

| DISCIPLINE | PRIMARY REVIEWER | SECONDARY REVIEWER |
|---|---|---|
| Application Technical Lead | Chunchun Zhang | NA |
| Drug Substance | Rajan Pragani | Su (Suong) Tran |
| Drug Product | Shrikant Pagay | Balajee Shanmugam |
| Microbiology | Renee Marcsisin | Jess Wells |
| Biopharmaceutics | Qi Zhang | Jing Li |
| Process | Lixia Cai | Dan Obrzut |
| Facility | Lixia Cai | Dan Obrzut |
| Regulatory Business Process Manager | Kristine Leahy | NA |
| ORA Lead | Caryn McNabb | NA |
| Environmental Assessment (EA) | Shrikant Pagay | Balajee Shanmugam |

# 1 Executive Summary

## 1.1. Application Summary Action

Tetracaine hydrochloride ophthalmic solution is one of several topical anesthetic products marketed for decades in the United States without an approved new drug application. Tetracaine is also known as amethocaine and pontocaine. The drug product facility is not in compliance with current good manufacturing practices, but the application is otherwise approvable. The application will receive a complete response action. The complete response action will recommend package insert changes identified in this review.

## 1.2. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Temporary anesthesia of the cornea and conjunctiva allow ophthalmic procedures to be performed because the patient will not have a touch or pain reflex and can remain still during the procedure. The localized anesthesia limits potential injuries to the local area anesthetized. The temporary duration limits long term risks.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • The cornea and conjunctiva have numerous touch and pain receptors. There are multiple ophthalmic procedures which require a patient to hold still in order to be completed. Patients will not hold still if their eye hurts. | Corneal and conjunctival anesthesia are required for patients to be able to hold still during ophthalmic procedures. |
| Current Treatment Options | • Tetracaine ophthalmic solution, lidocaine ophthalmic solution and proparacaine ophthalmic solution will provide corneal and conjunctival anesthesia. | Topical corneal and conjunctival anesthetics have been used for decades to provide corneal anesthesia. |
| Benefit | • The intended procedure can be completed. | Anesthesia interferes with the perception of pain and touch, minimizing pain during the procedure. |
| Risk and Risk Management | • Corneal and conjunctival anesthesia inhibit self defense reflexes and healing mechanisms of the cornea and conjunctiva. | The short-term duration and localized area of effect limit potential injuries. |

### 1.3. Patient Experience Data

This product causes topical, local anesthesia resulting in a temporary (20 minutes) absence of sensation at the site of application.

Patient Experience Data Relevant to this Application (check all that apply)

| | | | | |
|---|---|---|---|---|
| √ | The patient experience data that was submitted as part of the application, include: | | | |
| | √ | Clinical outcome assessment (COA) data, such as | | |
| | | | √ | Patient reported outcome (PRO) |
| | | | □ | Observer reported outcome (ObsRO) |
| | | | √ | Clinician reported outcome (ClinRO) |
| | | | □ | Performance outcome (PerfO) |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | |
| | □ | Observational survey studies designed to capture patient experience data | | |
| | □ | Natural history studies | | |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | |
| | □ | Other: (Please specify) | | |
| □ | Patient experience data that was not submitted in the application, but was considered in this review. | | | |

## 2 Therapeutic Context

### 2.1. Analysis of Condition

Topical anesthesia is desired to effectively perform a number of ophthalmic examinations and procedures. Ideally, the anesthetic agent can be easily applied, will provide effective anesthesia throughout the procedure and has a duration of action that minimizes the risks of patient self-injury after the procedure is complete.

### 2.2. Analysis of Current Treatment Options

| Tradename | Established Name | NDA Number | Indication |
|---|---|---|---|
| Tetracaine | Tetracaine ophthalmic solution, 0.5% | NDA 208-135 | For procedures requiring a rapid and short-acting topical ophthalmic anesthetic |
| Alcaine | Proparacaine ophthalmic solution, 0.5% | ANDA 80-027<br>ANDA 80-027<br>ANDA 40-277<br>ANDA 87-681<br>ANDA 40-074 | For topical anesthesia in ophthalmic practice. |
| Akten | Lidocaine ophthalmic gel, 3.5% | **NDA** 22-221 | For local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures |

### 2.3. Alternative Tetracaine Ophthalmic Products

**COMPOSITION OF THE DRUG PRODUCT:**

| Component | NDA 210182 Amount (% w/v) | NDA 208135 Amount (% w/v) | Function |
|---|---|---|---|
| Tetracaine Hydrochloride | 0.5% (b) (4) | 0.5* (b) (4) | Active |
| Boric Acid | (b) (4) | (b) (4) | (b) (4) |
| Edetate disodium (b) (4) | | | |
| Sodium Acetate (trihydrate) | | | |
| Sodium chloride | | | |
| Potassium chloride | | | |
| Chlorobutanol | 0.4% (b) (4) | | Antimicrobial Preservative |
| Hydrochloric acid and/or sodium hydroxide | Target pH (b) (4) | | pH Adjustor |
| Acetic acid and/or sodium acetate | | Target pH of 4.5 | pH Adjustor |
| Water for Injection | qs to 100% | qs to 100% | Vehicle |

## 3 Regulatory Background

Tetracaine Hydrochloride is a topical anesthetic used since at least the 1930s. While several different formulations have been successfully used to anesthetize the eye, the formulation which is the subject of this NDA, Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% was originally developed by Pharmafair, Inc. in Happauge, NY. Bausch & Lomb (B&L) purchased the product and transferred it, as is, to the Tampa, Florida manufacturing facility in 1992. The product formulation and specifications were maintained throughout the technology transfer, and there have been few changes since 1992. In 1997, a (b) (4) preservative (chlorobutanol) was added to account (b) (4) the active pharmaceutical ingredient in the formulation was maintained to utilize the vast amount of historical data available to support

this NDA. The 0.5% label claim remains the same to comply with the historically labeled product. In addition, alternate drug substance suppliers were validated in 1994 and in 2005. The current drug substance manufacturer (b) (4) has been the sole source of drug substance since 2005.

Tetracaine has been reported to be self-preserving in the literature. The effectiveness of the preservative (chlorobutanol) has been investigated at approximate concentrations of 0%, 5%, 10%, 20%, 80%, 100% and 120% of label claim (0.4%). The formulation was found to meet all requirements of antimicrobial effectiveness testing, USP <51> at each of the above referenced concentrations. Passing USP <51> with a chlorobutanol concentration of zero is equivalent to a self-preserving solution. While the drug product is sufficiently self-preserving to pass the USP test requirement, testing of formulations with 5% of the chlorobutanol label claim or higher demonstrated a higher kill effectiveness.

# 4 Significant Issues from Other Review Disciplines

## 4.1. Office of Scientific Investigations (OSI)

The clinical portion of the application is based on published literature studies. Based on the large number of consistent study results and the widespread use of this product in clinical practice, no inspections were requested from OSI.

## 4.2. Clinical Microbiology – N/A

# 5 Summary of Office of Pharmaceutical Quality

Satisfactory information and responses have been submitted to support the drug substance, drug product, quality micro, manufacturing process, and biopharmaceutics aspects. At the current time, GMP inspection of the manufacturing facilities supporting the NDA application indicates lack of compliance and OPF has issued an overall recommendation of "Withhold." In particular, the compliance status of the drug product manufacturing facility, Bausch & Lomb (FEI 1000113778), was found unacceptable and the Office of Compliance further confirmed the OAI classification through email communication on 11/1/2018. In agreement with the above recommendation, NDA 210821 is recommended for Complete Response from Product Quality perspective. Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

The following CR statement about the unacceptable manufacturing facility (Bausch & Lomb) should be included in the CR letter:

> *During a recent inspection of the Bausch & Lomb (FEI 1000113778) manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of*

*the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.*

Release and shelf life specifications for Tetracaine Hydrochloride Ophthalmic

| Test | Procedure | Acceptance Criteria | |
|---|---|---|---|
| | | Release | Shelf Life (Stability) |
| Description | Visual (b) (4) | Colorless to slightly yellow solution. | Colorless to slightly yellow solution. |
| (b) (4) | | | |

# 6 Nonclinical Pharmacology/Toxicology

The applicant is relying on the 45-year marketing history of tetracaine and has not conducted any non-clinical studies to support the application. As a short acting, topical anesthetic with negligible systemic absorption, there are no carcinogenic, teratogenic or systemic toxicity questions that need to be addressed by nonclinical studies. Local toxicity issues and pharmacodynamics studies are better addressed by the human clinical studies available in the literature than by non-clinical studies.

# 7 Clinical Pharmacology/Biopharmaceutics

The applicant did not conduct any clinical pharmacology related studies and requested the waiver of evidence of in vivo bioavailability or bioequivalence. In accordance with the 21 CFR §320.22(e), the Biopharmaceutics reviewer recommended granting the waiver of evidence of in vivo bioavailability or bioequivalence to this NDA on the basis of the compatibility with the protection of public health due to its long history of clinical use. I concur with the waiver.

# 8 Clinical Pharmacology

The drug product is topically applied to the cornea. There is little or no measurable systemic absorption.

# 9 Sources of Clinical Data and Review Strategy

Clinical Studies

All literature reports submitted by the Applicant were reviewed to determine if the design and results of the study supported the use of tetracaine 0.5% as a topical ophthalmic anesthetic. Studies in which the tetracaine ophthalmic solution is a 0.5% concentration, a formulation consistent with the one proposed in this NDA and either having an unidentified source or identified as being sourced by Valent, Bausch & Lomb or Pharmafair are included in the first table below and used to support this application. Studies in which the tetracaine ophthalmic solution is identified as specifically being sourced by a company other than Valent, Bausch & Lomb or Pharmafair have been identified and included in a second table below because they are used to support this application.

| Study | Design | Objective | Subjects | Treatment | B&L Product |
|---|---|---|---|---|---|
| Barequet 1999 | Randomized | To compare the efficacy of lidocaine with tetracaine for topical anesthesia in clear corneal cataract surgery | 25 | Single application of lidocaine 2% gel or 1 drop of 0.5% tetracaine | Unknown |
| Blaha 2011 | Prospective, masked, randomized | To compare the effectiveness of four different anesthetic methods for intravitreal injection | 24 | Proparacaine 0.5%<br>Tetracaine 0.5%<br>Lidocaine 4% pledget<br>Lidocaine 2% | Yes (Bausch and Lomb) |

| Study | Design | Objective | Subjects | Treatment | B&L Product |
|---|---|---|---|---|---|
| Carden 1998 | Randomized, controlled, observer masked | To test the effect of amethocaine on reducing postoperative pain, vomiting, and length of stay in children having strabismus repair | 62 (6 months–15 years) | 2 drops of 0.5% amethocaine*, subconjunctival bupivacaine 0.5%, or placebo (saline) | Unknown |
| Kim 2003 | Randomized, double-masked, placebo-controlled | To compare the effect of placebo to intraoperative 0.5% topical amethocaine or 0.5% topical ketorolac on pain control after strabismus surgery in children | 51 (2–7 years) | 2 drops of 0.5% amethocaine*, 0.5% ketorolac, or placebo (saline) at the start and end of strabismus repair surgery | Unknown |
| Nomura 2001 | Prospective, randomized | To evaluate corneal touch sensitivity measured by Cochet-Bonnet anesthesiometer | 17 | Tetracaine 0.5%<br>Lidocaine 4%<br>Bupivacaine 0.75%<br>Tetracaine & Lidocaine<br>Tetracaine & Bupivacaine | Unknown |
| Ogun 2014 | Prospective, randomized | To evaluate the potentiating effect of tetracaine on pupil dilation | 50 | Tetracaine<br>Placebo | Unknown |
| Sabermoghadam 2012 | pilot study | to find a new form of lidocaine to give a sufficient level of anesthesia | 30 | Tetracaine<br>Lidocaine cyclodextrin | Unknown |
| Sanabria 2013 | prospective, randomized, double-masked | to evaluate the efficacy of different anesthetics and topical anti-inflammatory treatment in patients undergoing intravitreal injection (IVI) | 156 | Tetracaine 0.5% +naphazoline<br>Lidocaine 5% | Unknown |
| Shafi 1998 | prospective, randomized, double masked | to evaluate the claim that topical proxymetacaine produces little or no discomfort on instillation by comparing it against topical amethocaine | 53 | Proxymetacaine 0.5%<br>Amethocaine* 0.5% | Unknown |
| Tsoumani 2010 | Randomized, controlled, double- masked | To compare the efficacy of tetracaine and the combination of lidocaine application and instillation of tetracaine as methods of topical anesthesia for cataract surgery | 51 | 0.5 cm lidocaine 2% gel plus 1 drop of 0.5% tetracaine or 1 drop of 0.5% tetracaine 5 min apart × 3 | Unknown |
| Yau 2010 | Randomized, observer masked | To compare anesthetic effectiveness of 3 topical agents for intravitreal injections | 93 | Tetracaine 0.5%<br>Cocaine 4%<br>Tetracaine 0.5% & Lidocaine pledget | Unknown |

* Tetracaine is also known as amethocaine and pontocaine.

Studies not used to assess safety and efficacy:

| Study | Design | Objective | Subjects | Treatment | B&L Product |
|---|---|---|---|---|---|
| Amiel 2007 | Randomized, double-masked | To assess the anesthetic efficacy of tetracaine versus lidocaine in routine cataract extraction | 100 | 1-inch ribbon of lidocaine 2% jelly or 1 drop of 0.5% tetracaine | No (Tetravisc) |
| Anninger 2007 | Randomized, double-masked | To test the effect of tetracaine on reducing the intensity and incidence of postoperative pain and emergence agitation after strabismus surgery in children | 88 (1–12 years) | 2 drops of 1% tetracaine before and after surgery with placebo (saline) controls | No (1% solution) |
| Chalam 2009 | randomized, muti-surgeon, controlled study | To compare the clinical efficacy of lidocaine 2% with tetracaine 0.5% for cataract surgery | 122 | lidocaine 2% tetracaine 0.5% | No (Ocusoft) |
| Harman 2000 | Non-masked | To determine whether lidocaine is as efficacious as tetracaine for obtaining ocular anesthesia in cataract surgery | 100 | 0.5-inch strip lidocaine 2% jelly or 2 drops of 0.5% tetracaine 10 min apart | No (Ciba Vision) |
| Moshifar 2014 | Prospective, single-masked, randomized | To evaluate the efficacy of proparacaine and tetracaine for pain control in patients undergoing LASIK and PRK | 256 eyes from 128 patients | Tetracaine 0.5% Proparacaine 0.5% | Tetracaine (Alcon) Proparacaine (B&L) |
| Rifkin 2012 | prospective, randomized | To determine factors associated with patient's comfort during routine in-office intravitreal injection. | 60 | Proparacaine 0.5% TetraVisc Tetracaine 0.5% | Tetravisc (Ocusoft) Tetracaine (Alcon) |
| Watson 1991 | Randomized, observer masked | To assess the effect of topical amethocaine on postoperative analgesia after strabismus surgery in children | 40 (1–12 years) | 2 drops of 1% amethocaine* versus placebo (saline) | No (1% solution) |
| Yu 2003 | Randomized, double-masked, double dummy | To compare the efficacy of lidocaine with amethocaine as the sole anesthetic agent for strabismus surgery | 14 | 1 mL lidocaine 2% gel in one eye and 1 drop of 1% amethocaine* 5 min apart × 3 in fellow eye | No (1% solution) |

* Tetracaine is also known as amethocaine and pontocaine.

The simple fact that cataract surgery, intraocular pressure measurements or intravitreal injections were able to be performed with tetracaine as the only anesthetic demonstrates the efficacy of tetracaine in producing an anesthetic effect. Each of the published studies describes successful surgery, injections or intraocular pressure measurements. As described in the regulations for adequate and well controlled studies, 21 CFR 314.126, patients could have been their own control (i.e., historical control) because anesthesia would not otherwise be expected to occur. The studies are not sufficiently powered to be able to establish comparative information between tetracaine,

proparacaine and lidocaine and therefore it is not possible to establish if any one of these is more effective than any of the other topical ophthalmic anesthetics.

## 10 Safety

The adverse event profile for tetracaine based on the published studies and postmarketing reporting suggest that the most common adverse events are transient events associated with instillation of the drop. These include events such as burning, stinging, discomfort, irritation and pain. Corneal toxicity with damage to the epithelium has also been reported to occur with abuse of anesthetics.

Safety information collected from current marketing
The safety data available for review does not allow for a quantitative determination of the exact incidence of each type of adverse reactions. Pooling of the safety results from the published reports and postmarketing data cannot be used to provide quantitative safety information.

In the post-marketing database, of the 357 reported reaction events, 182 were eye disorders, 43 of these events were instillation site reactions (erythema, pain, swelling). Of the non-ocular events 55 involved ineffective drug reports.

A summary of postmarketing safety data including spontaneous adverse reaction reports and reports in published literature with a cutoff date of January 16, 2018, is provided below. During the reporting period the company estimated that over 3 million units had been sold in the US.

There were 357 adverse reactions reported in 213 patients. The vast majority of these reports are eye disorders (n=182), 43 events were instillation site reactions (erythema, pain, swelling). Of the non-ocular events 55 involved ineffective drug reports. Of the total adverse reaction reports 189 patients were derived from spontaneous reports and 24 patients from the published literature or clinical studies.

Distribution data for Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% (2013-2016)

| NDC | Product | 2013 Units | 2014 Units | 2015 Units | 2016 Units | Total Units |
|---|---|---|---|---|---|---|
| 24208-0920-64 | Tetracaine Hydrochloride Ophthalmic Solution 0.5%, | (b) (4) | | | | |

Reported Adverse Reactions

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Drug ineffective | 41 | 35 | 6 |
| Instillation site pain | 37 | 36 | 1 |
| Eye irritation | 17 | 17 | 0 |

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Ocular hyperemia | 15 | 15 | 0 |
| Eye pain | 14 | 13 | 1 |
| Medication error | 11 | 11 | 0 |
| Corneal epithelium defect | 10 | 7 | 3 |
| Corneal edema | 10 | 7 | 3 |
| Drug ineffective for unapproved indication | 10 | 10 | 0 |
| Hypersensitivity | 7 | 7 | 0 |
| Iridocyclitis | 7 | 3 | 4 |
| Vision blurred | 7 | 7 | 0 |
| Conjunctival hyperemia | 6 | 4 | 2 |
| Pain | 6 | 2 | 4 |
| Visual impairment | 6 | 6 | 0 |
| Eye infection | 5 | 5 | 0 |
| Mydriasis | 5 | 4 | 1 |
| Punctate keratitis | 5 | 3 | 2 |
| Off label use | 4 | 4 | 0 |
| Prescription drug used without a prescription | 4 | 0 | 4 |
| Accidental Exposure to Product | 3 | 3 | 0 |
| Corneal disorder | 3 | 2 | 1 |
| Dermatitis allergic | 3 | 3 | 0 |
| Discomfort | 3 | 2 | 1 |
| Drug interaction | 3 | 3 | 0 |
| Eyelid edema | 3 | 3 | 0 |
| Photophobia | 3 | 3 | 0 |
| Anaphylactic reactions | 2 | 2 | 0 |
| Anaphylactic shock | 2 | 2 | 0 |
| Corneal abrasion | 2 | 1 | 1 |
| Corneal defect | 2 | 2 | 0 |
| Corneal opacity | 2 | 2 | 0 |
| Corneal pigmentation | 2 | 2 | 0 |
| Dizziness | 2 | 2 | 0 |
| Drug effect decreased | 2 | 2 | 0 |

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Eczema | 2 | 2 | 0 |
| Expired product administered | 2 | 2 | 0 |
| Eye swelling | 2 | 2 | 0 |
| Injection site pain | 2 | 2 | 0 |
| Lacrimation increased | 2 | 2 | 0 |
| No adverse event | 2 | 2 | 0 |
| Ocular discomfort | 2 | 2 | 0 |
| Sinus arrhythmia | 2 | 2 | 0 |
| Visual acuity reduced | 2 | 2 | 0 |
| Asthenia | 1 | 1 | 0 |
| Blindness | 1 | 1 | 0 |
| Blood pressure increased | 1 | 1 | 0 |
| Bradycardia | 1 | 1 | 0 |
| Burning sensation mucosal | 1 | 1 | 0 |
| Chemical burns of eyes | 1 | 0 | 1 |
| Circulatory collapse | 1 | 1 | 0 |
| Corneal decompensation | 1 | 0 | 1 |
| Corneal infiltrates | 1 | 0 | 1 |
| Corneal neovascularization | 1 | 1 | 0 |
| Corneal perforation | 1 | 1 | 0 |
| Corneal scar | 1 | 0 | 1 |
| Corneal thinning | 1 | 1 | 0 |
| Dermatitis contact | 1 | 1 | 0 |
| Diplopia | 1 | 1 | 0 |
| Drug effect incomplete | 1 | 1 | 0 |
| Drug effect prolonged | 1 | 1 | 0 |
| Drug screen positive | 1 | 1 | 0 |
| Dysgeusia | 1 | 1 | 0 |
| Dyspnea | 1 | 1 | 0 |
| Dystasis | 1 | 1 | 0 |
| Eczema weeping | 1 | 1 | 0 |
| Emotional distress | 1 | 1 | 0 |

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Endophthalmitis | 1 | 1 | 0 |
| Erythema | 1 | 1 | 0 |
| Eye disorder | 1 | 0 | 1 |
| Eye excision | 1 | 1 | 0 |
| Eye inflammation | 1 | 1 | 0 |
| Eye injury | 1 | 1 | 0 |
| Eyelid irritation | 1 | 1 | 0 |
| Fibrosis | 1 | 1 | 0 |
| Fluid retention | 1 | 1 | 0 |
| Foreign body in gastrointestinal tract | 1 | 1 | 0 |
| Foreign body sensation in eyes | 1 | 1 | 0 |
| Headache | 1 | 1 | 0 |
| Heart rate decreased | 1 | 1 | 0 |
| Hot flush | 1 | 1 | 0 |
| Hyperplasis | 1 | 1 | 0 |
| Hyperthermia malignant | 1 | 1 | 0 |
| Hypotension | 1 | 1 | 0 |
| Injection site erythema | 1 | 1 | 0 |
| Injection site pruritus | 1 | 1 | 0 |
| Injection site swelling | 1 | 1 | 0 |
| Iridocele | 1 | 1 | 0 |
| Laboratory test abnormal | 1 | 1 | 0 |
| Leukocytosis | 1 | 1 | 0 |
| Loss of consciousness | 1 | 1 | 0 |
| Malaise | 1 | 1 | 0 |
| Miosis | 1 | 1 | 0 |
| Mucous membrane disorder | 1 | 1 | 0 |
| Nausea | 1 | 1 | 0 |
| Neovascularization | 1 | 0 | 1 |
| Oropharangeal swelling | 1 | 1 | 0 |
| Palpitations | 1 | 1 | 0 |
| Periorbital edema | 1 | 1 | 0 |

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Pharyngeal edema | 1 | 1 | 0 |
| Product quality issue | 1 | 1 | 0 |
| Product use in unapproved indication | 1 | 1 | 0 |
| Pruritus | 1 | 1 | 0 |
| Rash generalized | 1 | 1 | 0 |
| Retching | 1 | 1 | 0 |
| Skin discoloration | 1 | 1 | 0 |
| Skin disorder | 1 | 1 | 0 |
| Skin exfoliation | 1 | 1 | 0 |
| Skin fissures | 1 | 1 | 0 |
| Skin test positive | 1 | 1 | 0 |
| Swelling | 1 | 1 | 0 |
| Swelling face | 1 | 1 | 0 |
| Swollen tongue | 1 | 1 | 0 |
| Syncope | 1 | 1 | 0 |
| Ulcerative keratitis | 1 | 1 | 0 |
| Under dose | 1 | 1 | 0 |
| Unresponsive to stimuli | 1 | 1 | 0 |
| Urticaria | 1 | 1 | 0 |
| Wheezing | 1 | 1 | 0 |

| | | | |
|---|---|---|---|
| Total AEs | 357 | 317 | 40 |
| Total Patients | 213 | 189 | 24 |

Financial Disclosure
Not applicable. All studies were literature based and did not identify the source of financial support for the study.

## 11 Advisory Committee Meeting

There were no issues identified that were believed to benefit from an advisory committee presentation and/or discussion. No advisory committee meeting was held.

## 12 Pediatrics

Published clinical studies included pediatric patients from birth through 17 years of age. There are no differences between pediatric patients and adult patients in anesthetizing the eye with tetracaine ophthalmic solution.

## 13 Risk Evaluation and Mitigation Strategies (REMS)

Based on the topical, local administration, short duration, negligible systemic absorption of this product and well recognized 70+ years of clinical use, no safety issues requiring mitigation strategies are warranted.

## 14 Postmarketing Requirements and Commitment

None.

# 15 Labeling Recommendations

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% safely and effectively. See full prescribing information for Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%.

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%, topical ophthalmic.
Initial U.S. Approval: 1965

——————INDICATIONS AND USAGE——————
Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%, is an ester local anesthetic indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic. (1)

——————DOSAGE AND ADMINISTRATION ———
One drop topically in the eye(s) as needed. (2)

——————DOSAGE FORMS AND STRENGTHS ———
Sterile, preserved, ophthalmic solution containing 0.5% tetracaine hydrochloride. (3)

——————CONTRAINDICATIONS ——————
Tetracaine Hydrochloride Ophthalmic Solution, 0.5% should not be used in patients with a history of hypersensitivity to any component of this preparation. (4)

——————WARNINGS AND PRECAUTIONS ———
- Do not use intracamerally since use may damage corneal endothelial cells. (5.1)
- Prolonged use or abuse may lead to corneal epithelial toxicity and may manifest as epithelial defects which may progress to permanent corneal damage. (5.2)
- Patients should not touch the eye for at least 10-20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye. (5.3)

——————————ADVERSE REACTIONS——————
Ocular adverse events: transient stinging, burning, conjunctival redness, eye irritation, eye pain, ocular discomfort. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb, a Division of Valeant Pharmaceuticals North America LLC,. at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*



*Sections or subsections omitted from the full prescribing information are not listed.

# FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic.

## 2 DOSAGE AND ADMINISTRATION

One drop topically in the eye(s) as needed.

## 3 DOSAGE FORMS AND STRENGTHS

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is a clear, colorless, ophthalmic solution containing 0.5% w/v tetracaine hydrochloride equivalent to tetracaine 0.44% w/v.

## 4 CONTRAINDICATIONS

Tetracaine Hydrochloride Ophthalmic Solution, USP, 0.5% should not be used in patients with a history of hypersensitivity to any component of this preparation.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Corneal Injury with Intracameral Use

Not for injection or intraocular use. Do not use intracamerally because use of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% may lead to damage of the corneal endothelial cells.

### 5.2 Corneal Toxicity

Prolonged use or abuse may lead to corneal epithelial toxicity and may manifest as epithelial defects which may progress to permanent corneal damage.

### 5.3 Corneal Injury due to Insensitivity

Patients should not touch the eye for at least 10-20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

## 6 ADVERSE REACTIONS

The following serious ocular adverse reactions are described elsewhere in the labeling:

- Corneal Injury with Intracameral Use [See Warnings and Precautions (5.1)]
- Corneal Toxicity [See Warnings and Precautions (5.2)]
- Corneal Injury due to Insensitivity [See Warnings and Precautions (5.3)]

The following adverse reactions have been identified following use of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliable estimate their frequency or establish a causal relationship to drug exposure.

Ocular Adverse Reactions
Transient stinging, burning, and conjunctival redness, eye irritation, eye pain, ocular discomfort.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% in pregnant women. Animal developmental and reproductive toxicity studies with tetracaine hydrochloride have not been reported in the published literature.

### 8.2 Lactation

Risk Summary

There are no data to assess whether Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is excreted in human milk or to assess its effects on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% and any potential adverse effects on the breastfed child from Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%.

### 8.3 Females and Males of Reproductive Potential

No human data on the effect of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% on fertility are available.

### 8.4 Pediatric Use

Safety of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% in the pediatric population has been demonstrated in clinical trials. Efficacy of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% for use in pediatric patients has been extrapolated from adequate and well controlled clinical trials in the adult population.

### 8.5 Geriatric Use

No overall differences in safety or effectiveness of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% have been observed between elderly and younger patients.

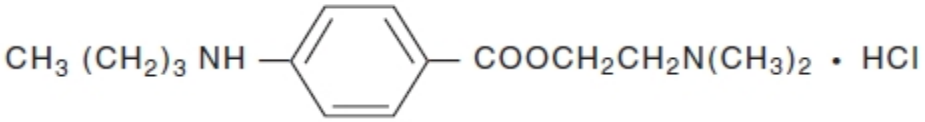
## 10 OVERDOSAGE

Prolonged use of a topical ocular anesthetic including Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% may produce permanent corneal opacification and ulceration with accompanying visual loss. (b) (4)

## 11 DESCRIPTION

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is a sterile, clear, colorless, topical local anesthetic for ophthalmic use containing tetracaine hydrochloride as the active pharmaceutical ingredient.

Tetracaine hydrochloride is chemically designated as benzoic acid, 4-(butylamino)-, 2-(dimethylamino) ethyl ester, monohydrochloride. Its chemical formula is $C_{15}H_{24}N_2O_2$ • HCl and it is represented by the chemical structure:



Tetracaine hydrochloride is a fine, white, crystalline, odorless powder with a molecular weight of 300.82

Active ingredient: tetracaine hydrochloride 0.5% w/v (equivalent to 0.44% w/v tetracaine)
Preservative: chlorobutanol 0.4%
Inactive ingredients: boric acid, potassium chloride, edetate disodium, water for injection USP. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH (3.7 – 6.0)

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Tetracaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses thereby affecting local anesthesia.

### 12.3 Pharmacokinetics

The systemic exposure to tetracaine following topical ocular administration of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% has not been studied. Tetracaine hydrochloride is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess the genotoxicity of tetracaine hydrochloride have not been reported in the published literature. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of tetracaine hydrochloride. Animal studies to assess the effects of tetracaine hydrochloride on fertility have not been reported in the published literature.

## 14 CLINICAL STUDIES

Topical administration of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% results in localized temporary anesthesia. The maximum effect is achieved within 10–20 seconds after instillation, with efficacy lasting 10–20 minutes. Duration of effect can be extended with repeated dosing. [See Corneal Toxicity (5.2) and Overdosage (10)].

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is supplied as a sterile, aqueous, topical ophthalmic solution with a fill volume of 15 mL in a 15 mL low-density polyethylene plastic dropper bottle with a low-density polyethylene dropper tip and white polypropylene cap.

NDC (b) (4)
Storage: Store at 15°C to 25°C (59°F to 77°F). Protect from light. Do not use if solution contains crystals, cloudy, or discolored. (b) (4)

## 17 PATIENT COUNSELING INFORMATION

Eye Care Precaution
Do not touch the dropper tip to any surface as this may contaminate the solution.
Advise patients that, due to the effect of the anesthetic, their eyes will be insensitive for up to 20 minutes and that care should be taken to avoid accidental injuries.

Manufactured for:
Paragon BioTeck, Inc.
4640 SW Macadam Ave, Ste 80
Portland, OR 97239

Manufactured and Distributed by:
Bausch & Lomb
8500 Hidden River Pkwy
Tampa, FL 33637
Revised: September 2017

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/
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WILEY A CHAMBERS
11/19/2018

WILLIAM M BOYD
11/19/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/BLA #:** | 210821 |
| **Drug Name:** | Tetracaine Hydrochloride Ophthalmic Solution 0.5% |
| **Indication(s):** | For procedures requiring a rapid and short acting ophthalmic anesthetic |
| **Applicant:** | Valeant Pharmaceuticals Ireland |
| **Date(s):** | Stamp Date: February 22, 2018 |
| | PDUFA Date: December 22, 2018 |
| **Review Priority:** | Standard |
| **Biometrics Division:** | DBIV |
| **Statistical Reviewer:** | Abel Tilahun Eshete, PhD |
| **Concurring Reviewers:** | Yan Wang, PhD |
| **Medical Division:** | Ophthalmology |
| **Clinical Team:** | Medical Reviewer: Jennifer Harris, MD |
| **Project Manager:** | Eithu Lwin: PharmD |

**Keywords:** Topical anesthesia, Pain scores, Tetracaine.

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# 1 EXECUTIVE SUMMARY

Valeant Pharmaceuticals Ireland (the Applicant) submitted this 505(b) (2) application seeking approval of a preserved tetracaine hydrochloride ophthalmic solution, 0.5% (hereafter referred to as Tetracaine 0.5%) as a rapid and short-acting topical ophthalmic anesthetic. The proposed dose and administration is one drop topically in the eye(s) as needed.

The applicant submitted fifteen key publications on prospective, randomized active/placebo-controlled studies to support the efficacy of Tetracaine 0.5%. The active controls used include: Lidocaine (at 2%, 4% and 5% concertation), Proparacaine, Proxymetacaine, Cocaine, Bupivacaine, and Oxybuprocaine. The 2% Lidocaine gel was the preferred comparator in six studies. Thirteen of the fifteen publications summarized active controlled only studies; while the remining two (Carden 1998 and Kim 2003) summarized studies that included both saline and an active control. Thirteen publications evaluated preserved (or not specified) formulations of Tetracaine 0.5% and two studies (Moshirfar 2014 and Lawerenson 1998) evaluated a non-preserved formulation. In the 15 studies combined, over 1000 subjects (aged 17-94 years) and, 122 children with an age range of 2 to 7 undergoing postoperative pain control following strabismus surgery, were included (Table 1).

The average pain score or the proportion of subjects who experienced little or no intraoperative and/or no postoperative pain, the rate of successful tonometry or corneal sensitivity were reported as efficacy endpoints in the published studies. Because the published studies used slightly different scales for pain measurement and evaluated different dosing regimens of Tetracaine 0.5% in patients undergoing different procedures, the reviewer did not perform a formal meta-analysis.

Three publications (Moshirfar 2014, Chalam 2009 and Rifkin 2009), in which a total of 209 subjects received at least one dose of Tetracaine 0.5%, reported statistically significant efficacy results in favor of Tetracaine 0.5% (Table 2). However, the results in two of these publications (Rifkin 2009 and Moshirfar 2014) should be interpreted with caution. The results in Moshirfar 2014 were not adjusted for multiple comparisons; and in Rifkin 2009, the reviewer's pairwise comparison of Tetracaine 0.5% with the other two treatment groups did not show statistically significant differences.

Two studies (Shafi 2008 and Nomura 2001) provided mixed efficacy evidence. Per Shafi 2008, compared Proxymetacaine, subjects who received Tetracaine 0.5% had numerically higher tonometry success rate; however, they also had a statistically significant higher mean stinging duration and discomfort scores. Nomura 2001 reported that, although a more comfortable anesthesia before instillation was obtained using one drop of Tetracaine 0.5%, Lidocaine 4% had longer corneal anesthesia compared to Tetracaine 0.5%.

The reported treatment differences were not statistically significant; either between Tetracaine 0.5% and saline (Carden 1998 and Kim 2003) or between Tetracaine 0.5% and 2% Lidocaine gel (Amiel 2007, Barequet 2000, Harman 2000). It is noted that, in the three active controlled

studies (Amiel 2007, Barequet 2000, Harman 2000), the observed average postoperative pain scores or the proportion of subjects with little or no pain in the Tetracaine 0.5% group were comparable to the corresponding figures in the 2% Lidocaine gel group. Likely based on these numerical similarities, the authors in these studies concluded that Tetracaine 0.5% is as effective as 2% Lidocaine gel. From a statistical perspective, however, an equivalence claim can only be made based on a pre-specified and justified equivalence margin, which was not the case in these studies. Therefore, the evaluation of the clinical relevance of these findings is deferred to the clinical reviewer.

Three studies (Sanabria 2013, Tsoumani 2010 and Yau 2011) evaluated the efficacy of Tetracaine 0.5% in combination with other products and reported treatment differences that were not statistically significant [Tetracaine 0.5% + Naphazoline vs. Lidocaine 5% (Sanabria 2013); Tetracaine 0.5% vs. Tetracaine 0.5% + Lidocaine 2% (Tsoumani 2010); Tetracaine 0.5% vs. Tetracaine 0.5% + Lidocaine 4% and Cocaine 4% (Yau 2011)].

With respect to safety, the applicant provided a safety summary from 16 key published studies that evaluated 0.5% or 1% solution of tetracaine administered by eye drops to induce local anesthesia. Among the 16 safety studies, 12 studies evaluated preserved (or not specified) formulations of tetracaine and 4 studies evaluated non-preserved formulations. In addition, the applicant provided a safety summary from three more publications (Havener 1983, McGee 2007, Weaver 2003) that investigated the toxicities of commonly used topical ocular anesthetics. Moreover, the applicant provided a summary of post marketing safety data from their safety database, with a cutoff date of January 16, 2018.

The most common adverse events reported in the published studies included: stinging, burning, conjunctival redness, eye irritation, eye pain, ocular discomfort and potential punctate corneal erosion. Serious adverse events were not reported in any of the studies provided in this application. In the post-marketing safety database, 357 adverse events by 213 patients were reported. Most of the adverse events reported were eye disorders (111 with 23 serious) or general disorders (107 with 7 serious). Deference is made to the clinical reviewer to determine whether the follow-up times and sample sizes of these studies allow ruling out of clinically meaningful safety (Table 3).

In conclusion, statistically significant lower average pain scores in the Tetracaine 0.5% arm were reported in three studies. However, the results from two of these three studies should be interpreted with caution. Efficacy results of Tetracaine 0.5% were also numerically comparable with the active controls in three additional studies. However, because there was no pre-specified and justified equivalence margin, the reviewer was not able to evaluate the equivalence claim made in these studies. Regarding safety, adverse events such as endophthalmitis, eye pain, and eye irritation after multiple administrations have been reported. Therefore, the overall risk-benefit of this product needs to be evaluated from a clinical perspective. This reviewer thus defers the assessment of the overall risk-benefit for this product and the subsequent decision to recommend for approval to the clinical review team.

*Reviewer's remark: The applicant is planning to develop a preserved formulation of Tetracaine 0.5%. However, some of the publications submitted in support of efficacy and safety evaluated a non-preserved formulation and some publications did not specify whether a preserved or non-preserved formulation is evaluated. This reviewer thus defers the determination of which studies are relevant to the evaluation of the current product to the clinical team.*

*Reviewer's remark: This submission has four more new publications (Blaha 2011, Nomura 2001, Lawerenson 1998, and Yau 2011) in addition to the nine publications used as a basis for approval of Tetracaine under NDA208135. Besides, two publications (Sanabria 2013, Tsoumani 2010) that were part of the submission for NDA208135 but were not counted in the nine main publications because both evaluated a combination of tetracaine with another product are included among the fifteen publications this NDA considered as key evidence. None of the six additional publications provided new efficacy evidence in favor of Tetracaine 0.5%. In fact, Lawerenson 1998 and Nomura 2001 reported that Proparacaine 0.5% and Lidocaine 4% produced less discomfort and longer corneal anesthesia, respectively, compared to Tetracaine 0.5%.*

# 2 Introduction

## 2.1 Overview

Per the Applicant, the drug product investigated in this 505(b) (2) NDA submission is the same product and formulation that was previously marketed by Bausch & Lomb since 1992. They state that, this product is a sterile, preserved ophthalmic solution presented in a 15-mL plastic bottle with dropper. This NDA depends solely on publication data to support the rapid and short acting topical ophthalmic anesthetic indication for Tetracaine 0.5%.

## 2.2 Data Sources and Quality

The full NDA can be accessed in the FDA electronic document room at the following link: \\CDSESUB1\evsprod\NDA210821. The applicant selected 15 publications to support their 505(b) (2) application. The active controls used alone or in combination with other products included Lidocaine (at 2%, 4% and 5% concertation), Proparacaine, Proxymetacaine, Cocaine, Bupivacaine, and Oxybuprocaine. The 2% lidocaine gel was the preferred comparator in six studies. A search on CDER Drugs@FDA did not provide approval information for Proxymetacaine and Oxybuprocaine. Using the same source, it is noted that, although lidocaine gel 2% was not approved at this concentration, higher dose of lidocaine (lidocaine 3.5% gel; NDA 22221) was approved for the indication of a topical local anesthetic for ophthalmic use. Proparacaine 0.5% was also approved for ophthalmic anesthetic use under NDA 12583. Bupivacaine (NDA 18053) is approved and is indicated for the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedure. GOPRELTO (cocaine hydrochloride) nasal solution is approved for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults (NDA 209963).

# 3 Statistical Evaluation

## 3.1 Evaluation of Efficacy

The design of the studies reported in the fifteen publications which served as a basis for this statistical review is presented in Table 1. Key findings from each publication is presented in Table 2. A detailed efficacy summary for each publication separately is presented in the appendix Section 5.1. In the 15 studies combined, over 1000 subjects (aged 17-94 years) and, 122 children with an age range of 2 to 7 undergoing postoperative pain control following strabismus surgery, were included.

Three of the fifteen studies (Moshirfar 2014, Chalam 2009 and Rifkin 2009) reported statistically favorable results for Tetracaine 0.5%. Two of these three studies used Proparacaine 0.5% as comparator and one used Lidocaine 2% gel. In the three studies combined, a total of 209 subjects received at least one dose of Tetracaine 0.5%. Rifkin 2009 reported that Tetracaine

0.5% has a statistically significant pain control (P<0.01) compared to the other two treatment arms (Proparacaine and TetraVisc). Subjects in the Tetracaine 0.5% arm had the lowest mean pain score (lower pain) (3.05±2.18) compared to Proparacaine (3.17±2.18) and TetraVisc (3.39±2.28). This reviewer's post-hoc pairwise comparison between Tetracaine 0.5% and Proparacaine (P=0.1245) and between Tetracaine 0.5% and TetraVisc (P=0.345) however did not show statistically significance difference for either of the two pairwise comparisons. Additionally, the ANOVA approach does not appear to account for possible dependence between measurements taken from the same subject. Therefore, the results from this study should be interpreted with caution.

Moshirfar 2014 reported a statistically significant pain control in favor of Tetracaine 0.5% at 30 minutes postoperative time. It is noted that the authors in this study preformed several treatment comparisons at different time points and for two different subgroups (LASIK and PRK). The reported P-values however were not adjusted for multiplicity; which should be taken into consideration when interpreting these findings. Two studies (Shafi 2008 and Nomura 2001)) provided mixed efficacy evidence. Shafi 2008 reported that, compared to Proxymetacaine, Tetracaine 0.5% had a statistically significant higher mean stinging duration (3.2 vs 22.1; P<0.001) and mean discomfort score (14.2 vs. 2.6; P=0.01) but also had higher tonometry success rate (98% vs 93%; P=0.08). Nomura 2001 reported that a more comfortable anesthesia was obtained using one drop of Tetracaine 0.5% before instillation. However, the same study also concluded that Lidocaine 4% provides longer corneal anesthesia compared to Tetracaine 0.5%.

The reported treatment differences were not statistically significant between Tetracaine 0.5% and saline (Carden 1998 and Kim 2003) and between Tetracaine 0.5% and Lidocaine 2% gel (Amiel 2007, Barequet 2000, Harman 2000). In these five studies combined, a total of 152 subjects received at least one drop of Tetracaine 0.5%. The authors in Amiel 2007, Barequet 2000, and Harman 2000 concluded that, Tetracaine 0.5% is as effective as Lidocaine gel 2%. Their conclusion seems to be informed by the numerically similar reported pain scores. The observed average postoperative pain scores or the proportion of subjects with little or no pain in the Tetracaine 0.5% group were comparable or slightly better relative to the Lidocaine group [(Mean Pain Score: 0.94 vs. 1.02: Amiel 2007); (Proportion of no pain: 90% vs. 90%: Herman 1999); (Proportion of no pain: 61.5% vs. 58.3%: Barequet 2000]. From a statistical perspective, however, an equivalence claim can only be made based on a pre-specified and justified equivalence margin, which was not the case in these studies.

There was also no statistically significant difference among four different anesthetic methods for intravitreal injection (Blaha 2011; P=0.65). The average combined pain scores for both the anesthesia and the intravitreal injection were 4.4 for the Lidocaine pledget, 3.5 for topical Proparacaine, 3.8 for the subconjunctival lidocaine injection, and 4.1 for topical Tetracaine 0.5%. There were also no statistical differences in the individual anesthesia or injection pain scores. Based on these results, the authors concluded that, topical anesthesia is an effective method for limiting pain associated with intravitreal injections.

Three studies (Sanabria 2013, Tsoumani 2010 and Yau 2011) evaluated a combination product of Tetracaine 0.5%. Sanabria 2013 reported that there was no statistically significant difference between Tetracaine 0.5% + Naphazoline versus Lidocaine 5%. Immediately after injection, the mean pain scores were 2.85±2.23 in the Tetracaine 0.5% + Naphazoline arm compared to 2.67±2.00 in the Lidocaine 5% group (P=0.727). The pain scores were 2.00±1.87 in the Tetracaine 0.5% + Naphazoline arm compared to 1.58±1.55 in the Lidocaine 5% group at 30 minutes after injection (P=0.210); and 1.81±2.23 in the Tetracaine 0.5% + Naphazoline arm compared to 1.81±2.23 in the Lidocaine 5% group 24 hours later (P=0979). Tsoumani 2010 reported that there was no statistically significance difference between Tetracaine 0.5% and a combination of Tetracaine 0.5% and Lidocaine 2% [Interoperative pain scores were 4.19 vs 3.99 and pain scores after one hour of surgery were 1.11 vs 1.58]. Yau 2011 reported that there was no statistically significance difference in patient reported average pain scores (P=0.549) among Tetracaine 0.5%, Tetracaine 0.5% + Lidocaine 4% and Cocaine 4%. The average patient reported pain scores were 21 (95% CI: 13, 29), 19 (95% CI: 12,26) and 21 (95% CI: 16, 27) in the Tetracaine 0.5%, Tetracaine 0.5% plus Lidocaine 4% and Cocaine arms, respectively.

In addition to the fifteen key publications, the applicant submitted additional 14 publications as supportive evidence. Of the additional publications, 10 summarized studies that evaluated the tetracaine ophthalmic solution 1% (Tetracaine 1%), one evaluated tetracaine ophthalmic solution 0.4% and the remaining three evaluated a combination product of Tetracaine 0.5% with other products (Please see Section 5.2 for further detail).

### 3.2 Evaluation of Safety

The Applicant has not conducted any clinical safety studies to support this NDA. They rely on published literature to demonstrate the safety of the drug product. Besides, they refer to the FDA's previous assessment of safety for Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT® (NDA 208135). The current NDA summarized safety information from studies published to date that have tested 0.5% or 1% solution of tetracaine administered by eye drops (one to three drops instillation) to induce local anesthesia. Additionally, a summary of post-marketing safety data from the Applicant's safety database with a cutoff date of January 16, 2018 is provided.

The study summaries indicate that no major safety concerns related to visual acuity or adverse events were reported in the reviewed studies. The most common adverse events reported in the published studies included: stinging, burning, conjunctival redness, eye irritation, eye pain, ocular discomfort and potential punctate corneal erosion. Serious adverse events were not reported in any of the studies provided in this application. In the post-marketing safety database, 357 adverse events by 213 patients were reported. Most of the adverse events reported were eye disorders (111 with 23 serious) or general disorders (107 with 7 serious). Deference is made to the clinical reviewer to determine whether the follow-up times and sample sizes of these studies allow ruling out of clinically meaningful safety.

# 4 Summary and Conclusions

## 4.1 Statistical issues

Because the published studies used slightly different scales for pain measurement and evaluated different dosing regimens of Tetracaine 0.5% in patients undergoing different procedures, the reviewer did not perform a formal meta-analysis. Additionally, in general, there are several limitations in relying on evidence from the published literature. These include the possibility of publication bias, lack of pre-specified protocols, non-standardized reporting of results, lack of study site inspections to ensure data quality, and lack of patient-level data with which to conduct independent analysis. Specific to the publications submitted in this NDA, only few of the publications had complete information that enabled the reviewer to perform further analysis and/or verify the reported results.

## 4.2 Conclusions and recommendation

In conclusion, statistically significant lower average pain scores in the Tetracaine 0.5% arm were reported in three studies. However, the results from two of these three studies should be interpreted with caution. Efficacy results of Tetracaine 0.5% were also numerically comparable with the active controls in three additional studies. However, because there was no pre-specified and justified equivalence margin, the reviewer was not able to evaluate the equivalence claim made in these studies. Regarding safety, adverse events such as endophthalmitis, eye pain, and eye irritation after multiple administrations have been reported. Therefore, the overall risk-benefit of this product needs to be evaluated from a clinical perspective. This reviewer thus defers the assessment of the overall risk-benefit for this product and the subsequent decision to recommend for approval to the clinical review team.

**Table 1: Publications evaluating analgesic efficacy of tetracaine ophthalmic solution 0.5%**

| Reference | Study Objectives | Total # of Patients | Dosing Regimen | Study Design |
|---|---|---|---|---|
| Chalam 2009 | To assess the comparative efficacy of topical Tetra Visc versus lidocaine gel 2% in cataract surgery | 122 | 5 drops of Tetra Visc (tertracaine 0.5%) or 5 doses of lidocaine gel 2% every five minutes | Randomized |
| Moshirfar 2014 | To compare the efficacy of tetracaine and proparacaine for pain control in laser in situ keratomileusis and photorefractive keratectomy | 128 | Single application of proparacaine or 1 drop of tetracaine 0.5% | Randomized, controlled, Single-masked |
| Rifkin 2000 | To determine factors that are associated with greatest patient comfort in intravitreal injection | 60 | Five monthly injection of 3× 1 drop of tetracaine 0.5% versus 1 drop of Tetra Visc versus 1 drop of proparacaine | Randomized |
| Shafi 1998 | To compare patient comfort following installation of topical proxymetacaine and amethocaine | 53 | 1 drops of amethocaine in one eye and one drop of proxymetacaine in the other eye | Randomize, double-masked |
| Amiel 2007 | To assess the anesthetic efficacy of tetracaine versus lidocaine in routine cataract extraction | 100 | 1-inch ribbon of lidocaine jelly 2% or 1 drop of tetracaine 0.5% | Randomized, double-masked |
| Barequet 1999 | To compare the efficacy of lidocaine with tetracaine for topical anesthesia in clear corneal cataract surgery | 25 | Single application of lidocaine gel 2% or 1 drop of tetracaine 0.5% | Randomized |
| Harman 2000 | To determine whether lidocaine is as efficacious as tetracaine for obtaining ocular anesthesia in cataract surgery | 100 | 0.5-inch strip lidocaine jelly 2% or 2 drops of tetracaine 0.5% 10 min apart | Non-masked |
| Carden 1998 | To test the effect of tetracaine on reducing postoperative pain, vomiting, and length of stay in children having strabismus repair | 62 | 2 drops of tetracaine 0.5%, subconjunctival bupivacaine 0.5%, or placebo (saline) | Randomized, controlled, observer masked |
| Kim 2003 | To compare the effect of placebo to intraoperative topical tetracaine 0.5% (amethocaine) or topical ketorolac 0.5% on pain control after strabismus surgery in children | 51 | 2 drops of tetracaine 0.5%, ketorolac 0.5%, or placebo (saline) at the start and end of strabismus repair surgery | Randomized, double-masked, placebo-controlled |
| Tsoumani 2010 | To compare the effect of 2 drops of tetracaine 0.5% alone or tetracaine 0.5% + lidocaine gel in pain control | 51 | 2 drops of tetracaine 0.5% alone or tetracaine 0.5% + lidocaine gel | Randomized, controlled |
| Yau 2011 | To compare the effects of 1-2 drops of tetracaine 0.5% alone, 4% lidocaine, tetracaine 0.5% +4% lidocaine or 4% Cocaine in patients receiving intravitreal injection | 93 | 1-2 drops of tetracaine 0.5%, 4% lidocaine, tetracaine 0.5% +4% lidocaine or 4% Cocaine | Randomized, triple-armed, double-blinded |
| Sanabria 2013 | To compare the effect of 1 drop of tetracaine 0.5% + naphazoline | 156 | 1 drop of tetracaine 0.5% + naphazoline | Randomized, double-masked |

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|---|---|---|---|---|
| | with 5% lidocaine in patients receiving intravitreal injection | | or 5% lidocaine | |
| Lawrenson 1998 | To compare the tolerability, and the depth and duration of corneal anesthesia of 0.4% oxybuprocaine, 0.5% amethocaine and 0.5% proxymetacaine | 14 | One drop of 0.4% oxybuprocaine, 0.5% amethocaine or 0.5% proxymetacaine | Randomized |
| Nomura 2001 | To compare the topical effects of tetracaine, lidocaine and bupivacaine on corneal sensitivity in normal eyes | 17 | 1-2 drops of tetracaine, lidocaine or bupivacaine | Randomized |
| Blaha 2011 | To evaluate the effectiveness of 4 different anesthetic methods. | 24 | 1 drop of proparacaine 0.5%, tetracaine 0.5%, lidocaine 4% or subconjunctival lidocaine 2% | Randomized, masked, controlled |

Source: Reviewer's Summary based on submitted publications

**Table 2: Summary of key findings from publication evaluating Tetracaine 0.5%**

| Reference | Pain Measurement Scale | Summary of Key Results |
|---|---|---|
| Chalam 2009 | Visual analog pain scale (0-10):<br>0 = no pain<br>10 =agonizing pain | A statistically significant difference in mean visual analog pain score (0.7+0.32 vs. 1.8+0.31; diff (95% CI) -1.1 (-1.21, -0.99); p<0.001) |
| Moshirfar 2014 | Pain severity scale:<br>0 = no pain<br>5 = moderate pain<br>10=severe pain | There was no statistically significant difference in mean pain score during surgery (1.6±0.2 vs. 1.2±0.2; p=0.067) and immediately after surgery (0.9±0.1 vs. 0.9±0.1; p=0.600) but there was a statistically significant difference in mean pain score 30 minutes post-surgery (1.3±0.1 vs. 2.2±0.1; diff (95% CI) -0.8 (-1.2, -0.50); p<0.001) |
| Rifkin 2009 | Visual analog pain scale (0-10):<br>0 = no pain<br>10 =agonizing pain | There was a statistically significant difference in mean pain scores between tetracaine and the other two (Tetracaine: 3.05±2.01vs. Tetra Visc: 3.39±2.26 vs. Proparacaine: 3.17±2.18; p<0.01). Pairwise comparisons however did not show statistical significance differences. Diff (95% CI): Tetracaine vs. Proparacaine: -0.34 (-0.94, 0.26); Tetra Visc vs. Proparacaine: -0.22 (-0.84, 0.40) |
| Shafi 1998 | Descriptive discomfort score:<br>0 = no pain<br>1 = mild pain<br>2 = moderate pain<br>3=severe pain<br>4=very severe pain | There was a statistically significant difference in mean descriptive discomfort score (14.2 vs. 2.6; p=0.01) and there was a numerically favorable but statistically non-significant difference in tonometry success rate (98% vs 93%; diff (95% CI): 5% (-2.3%, 13.6%); p=0.08) |
| Amiel 2007 | Pain scale (PRO):<br>0 = no pain/discomfort<br>1 = mild pain/discomfort<br>3 = moderate pain/discomfort<br>5=severe pain/discomfort | There was no statistically significant difference in mean postoperative pain scores (TetraVisc: 0.94 vs. Lidocaine gel 2%: 1.02; p=0.760) |
| Barequet 1999 | Cochet–Bonnet aesthesiometer (0-6):<br>0 = no sensation<br>6 =maximum sensation<br>Pain scale:<br>0 = no pain<br>1 = minimal pain<br>2 = moderate pain | There was no statistically significant difference in the proportion of patients with a grade of zero five minutes after application of the topical anesthesia (100% vs. 92%; diff (95% CI): 8.0% (-7.3%, 24.0%)). There was also no significant difference in proportion of subjects with pain score of 0 or 1 (satisfactory comfort) (61.5% vs. 58.3%; diff (95% CI): 3.2% (-30.5%, 41.6%)) |

| | | |
|---|---|---|
| | 3=significant pain | |
| Harman 2000 | Pain scale:<br>0 = no pain<br>1 = mild pain<br>2 = moderate pain<br>3=severe pain | There was no statistically significant difference in the proportion of patients with a score of zero (no pain) during surgery (90% vs. 90%; diff (95% CI): 0.0% (-11.7%, 11.7%)) |
| Carden 1998 | Modified Wong-Baker scale:<br>0 = Nil<br>1 = mild<br>2 = moderate<br>3=severe | There was no statistically significant difference at all measurement time points (30, 60, 120 and 180 minutes). Only plots and p-values were provided (0.240, 0.680, 0.07, and 0.390 respectively) |
| Kim 2003 | Modified children hospital of eastern Ontario pain scores (CHEOPS) | There was no statistically significant difference in mean (range) pain score (5 (4-9) vs. 5 (4-9) and mean anesthesia time (60±12 vs. 57±13; diff (95% CI): 3 (-5.4, 11.4)) versus placebo |
| Tsoumani 2010 | Visual analog pain scale (0-10):<br>0 = no pain<br>10 =agonizing pain | There was also no statistically significant difference between the two treatment groups in the mean intraoperative (Mean Score: 4.19 vs 3.88; P=0.663) and postoperative pain score (Mean Score: 1.11 vs. 1.58; 0.312). |
| Yau 2011 | A 100-mm Visual Analogue Scale (VAS) and Wong-Baker Faces | There was no statistically significant difference in VAS pain score (P=0.549) among the treatment arms. The mean VAS pain score for 0.5% tetracaine hydrochloride + 4% lidocaine pledget, 0.5% tetracaine hydrochloride drops alone and 4% cocaine (epinephrine 1/100 000) drops were respectively: 19 (95% confidence interval [CI] 12–26), 21 (95% CI 13–29), and 21 (95% CI 16–27). The mean Wong-Baker pain scores were 1.9 (95% CI 1.3–2.6), 2.1 (95% CI 1.4 –2.7), and 2.3 (95% CI 1.6 –3.1), respectively. |
| Sanabria 2013 | A Visual Analogue Scale (0-100) | There was no significant difference in mean pain score between the two treatment arms immediately after injection (P=0.727) and at 30 minutes post injection (P=0,210) and 24 hours after injection (P=0.979). The Means (SD) pain scores for tetracaine plus naphazoline arm were 2.85 (2.23), 2.00 (1.87) and 1.81 (2.23) immediately after injection, after 30 and after 24 hours, respectively. The corresponding values for the lidocaine arm were 2.67 (2.00), 1.58 (1.55) and 1.77 (2.09). |
| Lawrenson 1998 | Ten-point arbitrary comfort scale | There was no significant difference between the topical ocular anaesthetic drugs (0.4% oxybuprocaine, 0.5% amethocaine or 0.5% proxymetacaine) for the percentage of subjects achieving total anaesthesia at any time point. |
| Nomura 2001 | Cochet-Bonnet anesthesiometer | There was statistically significant difference between 4% lidocaine and 0.75% bupivacaine and 0.5% tetracaine + 0.75% bupivacaine (P<0.0005) with 4% lidocaine having a better effect. There was also a significant difference between 0.75% bupivacaine and 0.5% tetracaine + 4% lidocaine (p < 0.005). In this comparison, 0.5% tetracaine + 4% lidocaine had a better anesthetic effect. |
| Blaha 2011 | A visual analogue scale (0-10) | There was no statistically significant difference (P =0.28) between the pain scores from intravitreal injection. The average pain of the intravitreal injection was 3.0 with 4% lidocaine pledget (range, 0-9), 2.8 with topical proparacaine (range, 0-8), 2.3 with 2% lidocaine subconjunctival |

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|---|---|---|
| | | injection (range, 0-6), and 3.1 with topical tetracaine (range, 0-10). Similarly, there was no statistically significant difference (P = 0.17) between the pain scores for anesthesia. The average pain score from the anesthesia itself was 1.4 for 4% lidocaine pledget (range, 0-8), 0.7 for topical proparacaine (range, 0-4), 1.6 for 2% lidocaine subconjunctival injection (range, 0-6), and 1.0 for topical tetracaine (range, 0-4). |

Source: Reviewer's summary based on submitted publications

**Table 3: Safety summary from post-marketing data**

| Preferred term | Total AEs | Spontaneous | Literature/ Clinical Trials |
|---|---|---|---|
| Accidental Exposure to Product | 3 | 3 | 0 |
| Anaphylactic reactions | 2 | 2 | 0 |
| Anaphylactic shock | 2 | 2 | 0 |
| Asthenia | 1 | 1 | 0 |
| Blindness | 1 | 1 | 0 |
| Blood pressure increased | 1 | 1 | 0 |
| Bradycardia | 1 | 1 | 0 |
| Burning sensation mucosal | 1 | 1 | 0 |
| Chemical burns of eyes | 1 | 0 | 1 |
| Circulatory collapse | 1 | 1 | 0 |
| Conjuntival hyperemia | 6 | 4 | 2 |
| Corneal abrasion | 2 | 1 | 1 |
| Corneal decompensation | 1 | 0 | 1 |
| Corneal defect | 2 | 2 | 0 |
| Corneal disorder | 3 | 2 | 1 |
| Corneal epithelium defect | 10 | 7 | 3 |
| Corneal infiltrates | 1 | 0 | 1 |
| Corneal neovascularization | 1 | 1 | 0 |
| Corneal edema | 10 | 7 | 3 |
| Corneal opacity | 2 | 2 | 0 |
| Corneal perforation | 1 | 1 | 0 |
| Corneal pigmentation | 2 | 2 | 0 |
| Corneal scar | 1 | 0 | 1 |
| Corneal thinning | 1 | 1 | 0 |
| Dermatitis allergic | 3 | 3 | 0 |
| Dermatitis contact | 1 | 1 | 0 |
| Diplopia | 1 | 1 | 0 |
| Discomfort | 3 | 2 | 1 |
| Dizziness | 2 | 2 | 0 |
| Drug effect decreased | 2 | 2 | 0 |
| Drug effect incomplete | 1 | 1 | 0 |
| Drug effect prolonged | 1 | 1 | 0 |
| Drug ineffective | 41 | 35 | 6 |
| Drug ineffective for unapproved indication | 10 | 10 | 0 |
| Drug interaction | 3 | 3 | 0 |
| Drug screen positive | 1 | 1 | 0 |
| Dysgeusia | 1 | 1 | 0 |
| Dyspnea | 1 | 1 | 0 |

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|---|---|---|---|
| Dystasis | 1 | 1 | 0 |
| Eczema | 2 | 2 | 0 |
| Eczema weeping | 1 | 1 | 0 |
| Emotional distress | 1 | 1 | 0 |
| Endophthalmitis | 1 | 1 | 0 |
| Erythema | 1 | 1 | 0 |
| Expired product administered | 2 | 2 | 0 |
| Eye disorder | 1 | 0 | 1 |
| Eye excision | 1 | 1 | 0 |
| Eye infection | 5 | 5 | 0 |
| Eye inflammation | 1 | 1 | 0 |
| Eye injury | 1 | 1 | 0 |
| Eye irritation | 17 | 17 | 0 |
| Eye pain | 14 | 13 | 1 |
| Eye swelling | 2 | 2 | 0 |
| Eyelid irritation | 1 | 1 | 0 |
| Eyelid edema | 3 | 3 | 0 |
| Fibrosis | 1 | 1 | 0 |
| Fluid retention | 1 | 1 | 0 |
| Foreign body in gastrointestinal tract | 1 | 1 | 0 |
| Foreign body sensation in eyes | 1 | 1 | 0 |
| Headache | 1 | 1 | 0 |
| Heart rate decreased | 1 | 1 | 0 |
| Hot flush | 1 | 1 | 0 |
| Hyperplasis | 1 | 1 | 0 |
| Hypersensitivity | 7 | 7 | 0 |
| Hyperthermia malignant | 1 | 1 | 0 |
| Hypotension | 1 | 1 | 0 |
| Injection site erythema | 1 | 1 | 0 |
| Injection site pain | 2 | 2 | 0 |
| Injection site pruritus | 1 | 1 | 0 |
| Injection site swelling | 1 | 1 | 0 |
| Instillation site pain | 37 | 36 | 1 |
| Iridocele | 1 | 1 | 0 |
| Iridocyclitis | 7 | 3 | 4 |
| Laboratory test abnormal | 1 | 1 | 0 |
| Lacrimation increased | 2 | 2 | 0 |
| Leukocytosis | 1 | 1 | 0 |
| Loss of consciousness | 1 | 1 | 0 |
| Malaise | 1 | 1 | 0 |
| Medication error | 11 | 11 | 0 |
| Miosis | 1 | 1 | 0 |
| Mucous membrane disorder | 1 | 1 | 0 |
| Mydriasis | 5 | 4 | 1 |
| Nausea | 1 | 1 | 0 |
| Neovascularisation | 1 | 0 | 1 |
| No adverse event | 2 | 2 | 0 |
| Ocular discomfort | 2 | 2 | 0 |
| Ocular hyperemia | 15 | 15 | 0 |
| Off label use | 4 | 4 | 0 |

| | | | |
|---|---|---|---|
| Oropharangeal swelling | 1 | 1 | 0 |
| Pain | 6 | 2 | 4 |
| Palpitations | 1 | 1 | 0 |
| Periorbital edema | 1 | 1 | 0 |
| Pharyngeal edema | 1 | 1 | 0 |
| Photophobia | 3 | 3 | 0 |
| Prescription drug used without a prescription | 4 | 0 | 4 |
| Product quality issue | 1 | 1 | 0 |
| Product use in unapproved indication | 1 | 1 | 0 |
| Pruritus | 1 | 1 | 0 |
| Punctate keratitis | 5 | 3 | 2 |
| Rash generalized | 1 | 1 | 0 |
| Retching | 1 | 1 | 0 |
| Sinus arrhythmia | 2 | 2 | 0 |
| Skin discoloration | 1 | 1 | 0 |
| Skin disorder | 1 | 1 | 0 |
| Skin exfoliation | 1 | 1 | 0 |
| Skin fissures | 1 | 1 | 0 |
| Skin test positive | 1 | 1 | 0 |
| Swelling | 1 | 1 | 0 |
| Swelling face | 1 | 1 | 0 |
| Swollen tongue | 1 | 1 | 0 |
| Syncope | 1 | 1 | 0 |
| Ulcerative keratitis | 1 | 1 | 0 |
| Underdose | 1 | 1 | 0 |
| Unresponsive to stimuli | 1 | 1 | 0 |
| Urticaria | 1 | 1 | 0 |
| Vision blurred | 7 | 7 | 0 |
| Visual acuity reduced | 2 | 2 | 0 |
| Visual impairment | 6 | 6 | 0 |
| Wheezing | 1 | 1 | 0 |
| | | | |
| **Total AEs** | **357** | **317** | **40** |
| **Total Patients** | **213** | **189** | **24** |

Source: Applicant's summary

# 5 Appendix

## 5.1 Key publications evaluating tetracaine ophthalmic solution 0.5%

This section provides brief summaries of each of the nine publications that evaluated the analgesic efficacy of tetracaine ophthalmic solution 0.5%. Unless stated otherwise, all tables, figures and other summaries are taken from the results presented in the publications.

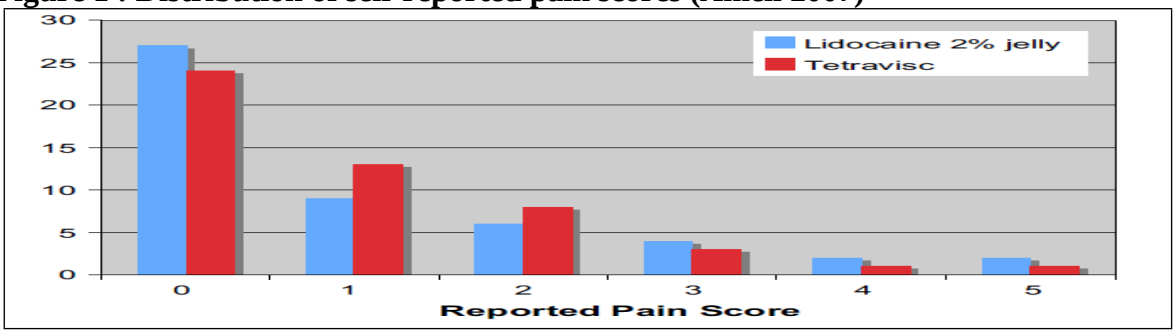
### 5.1.1 Amiel et al (2007): Tetracaine hydrochloride 0.5% versus lidocaine jelly 2% as a topical anesthetic agent in cataract surgery comparative clinical trial

This study was a prospective randomized double-blind clinical trial comprised of 100 patients having routine cataract extraction by clear corneal phacoemulsification. The objective of the study was to assess the anesthetic efficacy of tetracaine hydrochloride 0.5% (TetraVisc) versus lidocaine jelly 2% in routine cataract extraction.

In this study, patients were randomized to receive TetraVisc or lidocaine jelly 2%, applied once, approximately 5 minutes before surgery. Outcomes included a self-reported postoperative pain score and the need for supplemental anesthesia. Approximately 15 minutes after surgery, patients were asked to rate their intraoperative pain on a scale of 0 to 5(0=no pain/discomfort; 1=mild pain/discomfort; 3=moderate pain/discomfort; 5=severe pain/discomfort). The patient, surgeon, and technician collecting pain scores were all masked to the type of anesthesia used. Statistical analysis was performed using the 2-tailed Student t test.

There was no statistically significant difference in the mean self-reported postoperative pain score between TetraVisc and lidocaine jelly 2% (0.94 and 1.02, respectively; P =0.76). Due to lack of reported variability measures, the reviewer was not able to produce confidence interval for the estimated treatment differences. A single patient in the lidocaine group required supplemental anesthesia. The proportion of subjects who reported no pain or mild pain (0 or 1) were comparable between the TetraVisc and the lidocaine jelly 2% groups (36 (72%) vs. 37 (74%); diff: 2% (95% CI: -15.4%, 19.4%)). Slightly higher proportion of subjects in the lidocaine group 4(8%) reported greater than moderate pain compared to the TetraVisc group 2 (4%). The authors concluded that TetraVisc was as effective as lidocaine jelly 2% as a topical anesthetic agent for routine cataract extraction.

**Figure 1 : Distribution of self-reported pain scores (Ameil 2007)**



### 5.1.2 Harman (2000): Combined sedation and topical anesthesia for cataract surgery

This study was conducted to determine whether lidocaine jelly is as effective as tetracaine drops for obtaining ocular anesthesia and to evaluate sublingual lorazepam as premedication for sedation in cataract surgery. The study was divided in two phases. In the first phase of the study (the focus of this summary), 100 patients were divided into 2 groups of 50 each. The first 50 patients received 2 doses of tetracaine drops 10 minutes apart in the preoperative area. The next 50 patients received lidocaine jelly 2% in the conjunctival fornix 10 minutes before the patient was taken from the preoperative area to the operating room.

On the day after surgery, a questionnaire asked patients to determine whether they felt pain or pressure during cataract surgery; they were also asked when they felt normal sensation return to the eye after surgery. The patients were then asked to rank their pain or pressure from 0 to 3: 0=none, 1= mild, 2=moderate, and 3=severe. They were also asked to give the duration of anesthesia in minutes or hours. The proportion of subjects who reported no pain (score of zero) was 45 (90%) in both treatment groups. Slightly higher proportion of subjects in the tetracaine group reported mild and slightly lower proportion reported moderate pain compared to the lidocaine group (Mild: (4 (8%)) vs 3 (6%); Moderate: (1 (2%)) vs 2 (4%) ). Slightly higher proportion of subjects in the tetracaine group reported no pressure compared to subjects in the lidocaine group (45 (90%) vs 42 (84%); Table 4). The lidocaine 2% jelly group reported a relatively longer average duration of anesthesia (1 hour 40 minutes) compared to the tetracaine drops group of 42 minutes. The responses varied from 1 to 2 minutes to several hours.

The authors concluded that, lidocaine jelly 2% was as efficacious as topical tetracaine 0.5% drops for topical anesthesia in cataract surgery. They also indicated that lidocaine jelly is easier to use and administer and is significantly more cost-effective than tetracaine drops.

**Table 4: Summary pain and pressure scores (Harman 2000)**

| Measure | Group | |
|---|---|---|
| | Tetracaine N (%) | Lidocaine N (%) |
| Pain | | |
| None | 45 (90%) | 45 (90%) |
| Mild | 4 (8%) | 3 (6%) |
| Moderate | 1(2%) | 2 (4%) |
| Pressure | | |
| None | 45 (90%) | 42 (84%) |
| Mild | 5 (10%) | 8 (16%) |

### 5.1.3 Barequet et al (1999): Provision of anesthesia with single application of lidocaine gel 2%

This study included a preliminary toxicity study and a randomized study designed to compare the efficacy of a single application of lidocaine gel 2% with tetracaine 0.5% drops for topical anesthesia in clear corneal cataract surgery. In the randomized part of the study, 25 patients between the ages of 50-94 years were randomized in a 1:1 ratio to receive either lidocaine gel 2% (12 subjects; 4 males and 8 females) or tetracaine drops (13 subjects; 1 male and 12 females). Twenty minutes after the conclusion of surgery the patients were asked to describe the comfort using a predefined scale (0=no pain, 1=minimal pain, 2=moderate pain, 3=significant pain). The surgeon's subjective impression of patient comfort and ease of surgery was also assessed using the same scale. Additionally, corneal sensation was measured with the Cochet-Bonnet aesthesiometer before any medicine was applied, 5 minutes after application of the topical anesthesia, and at the conclusion of surgery. In this study, patient level data for comfort score and corneal sensitivity was provided.

The proportion of subjects who reported a satisfactory comfort level (grade 0 or 1) was 61.5% in the tetracaine group and 58.3 % in the lidocaine gel group (Diff: 3.2% (95% CI: -35.2%, 41.6%)). The corresponding values as reported by the surgeon were also 61.5% in the tetracaine group and 58.3 % in the lidocaine gel group. Two eyes in the lidocaine gel group (17%) and 4 (31%) in the tetracaine drops group received additional local anesthesia (P=0.64).

The median preoperative corneal sensitivity was 5 in the lidocaine gel group and 6 in the tetracaine drops group. Five minutes after application of the topical anesthesia and at the conclusion of surgery, the median values were 0 in both groups.

The authors concluded that a single preoperative application of lidocaine 2% gel provided satisfactory patient comfort to conduct safe clear corneal cataract surgery with IOL implantation and was comparable to the comfort achieved with multiple doses of tetracaine drops for topical anesthesia.

### 5.1.4 Carden (1998): Adjunctive intra-operative local anesthesia in pediatric strabismus surgery: A randomized controlled trial

This study was a prospective, randomized, three-armed clinical trial. The study involved treatment comparison between tropical amethocaine, sub-conjunctival bupivacaine and a normal saline (placebo). The purpose of this study was to test the hypothesis that adjunctive local anesthesia decreases post-operative pain, vomiting or length of stay in children having strabismus repair.

This study enrolled a total of 71 children between the ages of 54-71 Months who were booked for planned day surgery squint repair and whose patients consented to the study. The children

were randomized in a 1:1:1 ratio to receive either 2 drops of 0.5% guttae amethocaine, or sub-conjunctival bupivacaine or a saline. All treatments were provided at the end of surgery before emergence from anesthetic. The study indicated that patients booked for planned inpatient stay for strabismus were excluded for the study; therefore, children with chronic disease severe enough to mandate overnight stay due to previously known comorbidities as well as strabismus were excluded.

Pain was assessed by masked nurses using a modified Wong-Baker faces pain rating scale (0=Nil, 1=mild, 2=moderate and 3=severe) at 30, 60, 120 and 180 minutes and hourly thereafter until discharge. The pain outcome is listed as the principal objective outcome measure. The number of vomiting, the need for additional medication, time of discharge and a score on whether or not the children opened their eyes comfortably (yes or No) was also recorded.

After nine children with missing data were excluded, data from 20 children in the amethocaine group and 21chidren each in the sub-conjunctival bupivacaine and saline groups was used for analysis. The summary results (Table 5–Table 7) show that there were no major differences among the three treatment groups in the distribution of children by gender, age, operative and anesthesia data.

The study reported that based on a chi-square test at each time point, there was no statistically significant differences among the three treatment groups in pain score at all measurement times (P=0.24, 0.68, 0.07 and 0.39 at 30, 60, 120 and 180 minutes respectively; Figure 2). Although it is not clearly specified in the study, it seems that the test compared the proportion of subjects with a zero pain score (no pain) among the three treatment groups. As can be seen in Figure 2, the proportion of subjects with no pain was consistently higher in the amethocaine group compared to the placebo group. The study also showed that, although not statistically significant, there was a trend in the amethocaine arm in which there were less severe pain (pain score of 2 or 3) at 120 minutes (Figure 3).

Per the authors, by chance, subjects randomized to the placebo group were on average a year older. They stated that it is possible that the treatment effect was missed because subjects in the placebo arm had a better pain tolerance than those in the treatment arm. They reported that due to the small sample size, they were not able to perform subgroup analysis by age group. Because only graphical summary and P-values were presented in this study, the reviewer was not able to conduct further analysis or verify the reported results for the primary objective outcome of pain score.

No significance differences were observed among the three treatment groups with respect to number of vomiting, eye opening and sedation scores (Figure 3). Based on an ANOVA test, the study reported that there was also no significant difference in the mean discharge time among the three treatment groups (P=0.16). The mean (SD) discharge times for the amethocaine, bupivacaine and saline group were 186 (37), 208 (45), and 186 (43) respectively.

The publication states that this study was terminated after evaluating the 62 subjects because of the unexpected small difference between any of the groups. They also noted that the sample size calculation has shown that a sample size of 62 could yield a clinically significant difference (if one was truly present) with reasonable statistical power. They stated that the measured effect differences at the interim analysis were too small to warrant continued recruitment to the trial. They also state that the power of the present study turned out to be lower than planned and a small positive treatment effect may have been the conclusion of a larger study. They stated that they did not believe that any difference in outcome found by larger study would be high enough to warrant routine use of either technique.

**Table 5: Patient demographics (Carden 1998)**

| Characteristics | Treatment | | |
|---|---|---|---|
| | Amethocaine N=20 | Bupivacaine N=21 | Saline N=21 |
| Age (months)* | 57±28 (55; 17-110) | 54±40 (55; 6-162) | 57±28 (60; 11-182) |
| Sex (M:F) | 11:9 | 10:11 | 9:12 |

*Data are presented as mean +SD; values in parentheses indicate median age and range, respectively

**Table 6: Operative data (Carden 1998)**

| Characteristics | Treatment | | |
|---|---|---|---|
| | Amethocaine N=20 | Bupivacaine N=21 | Saline N=21 |
| Duration of surgery (min)* | 63±19 (30-90) | 58±14 (40-85) | 65±35 (35-110) |
| Previous surgery (n) | 13 | 14 | 13 |
| No previous eye surgery | 2 | 3 | 3 |
| Other muscles | 4 | 2 | 3 |
| Intra-ocular surgery | 1 | 2 | 2 |
| No muscle operated on (n) | | | |
| One | 3 | 1 | 3 |
| Two | 16 | 17 | 17 |
| Four | 1 | 3 | 1 |
| Incision (n) | | | |
| Fornix | 4 | 8 | 6 |
| Limbus | 12 | 10 | 14 |
| Combination | 4 | 3 | 1 |
| Conjunctival sutures (n) | | | |
| Yes | 19 | 18 | 20 |
| No | 1 | 3 | 1 |

*Data are presented as mean +SD

**Table 7: Anastasia data (Carden 1998)**

| | Treatment | | |
|---|---|---|---|
| | Amethocaine N=20 | Bupivacaine N=21 | Saline N=21 |
| Premedication with oral midazolam (n) | | | |
| Yes | 3 | 5 | 7 |
| No | 17 | 16 | 14 |
| Agents used for induction of anesthesia (n) | | | |
| Halothane | 2 | 2 | 3 |
| Thiopentone | 10 | 9 | 5 |
| Propofol | 3 | 8 | 10 |
| Halothane and thiopentone | 5 | 2 | 2 |
| Halothane and propofol | 0 | 0 | 1 |
| Agents used for maintenance of anesthesia | | | |
| Halothane and nitrous oxide | 13 | 14 | 17 |
| Isoflurance and nitrous oxide | 7 | 7 | 4 |
| Prophylactic antiemetic | | | |
| Metocloparmide | 3 | 6 | 10 |
| Droperidol | 8 | 5 | 7 |
| No antiemetic | 9 | 10 | 4 |

**Figure 2 : Summary of pain scores (Carden 1998)**

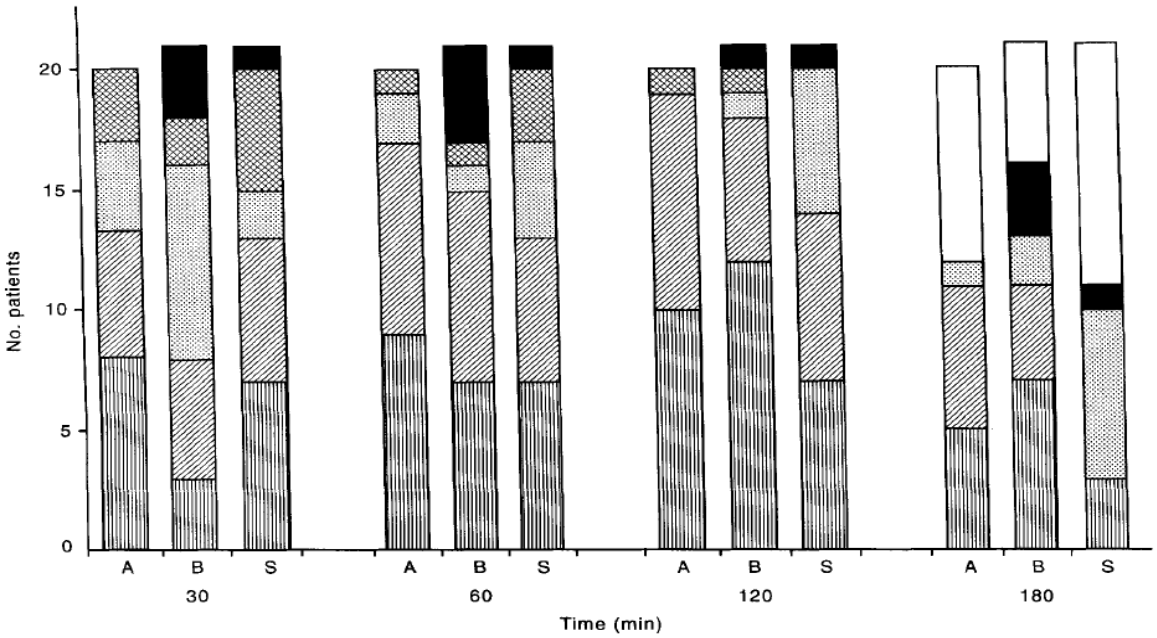



Figure 2. Pain scores (▥, 0; ▨, 1; ▩, 2; ■, 3) at each measured time following either topical amethocaine (A), sub-conjunctival bupivacaine (B) or topical normal saline (S) (Using Chi-squared analysis at each time assessment and excluding patients who were 'not recorded' (■) or 'discharged' (□). Comparing pain scores among the three treatments: 30 min $P = 0.24$; 60 min $P = 0.68$; at 120 min $P = 0.07$; 180 min $P = 0.39$.)

**Figure 3: Summary of pain scores (Mild versus Severe) (Carden 1998)**

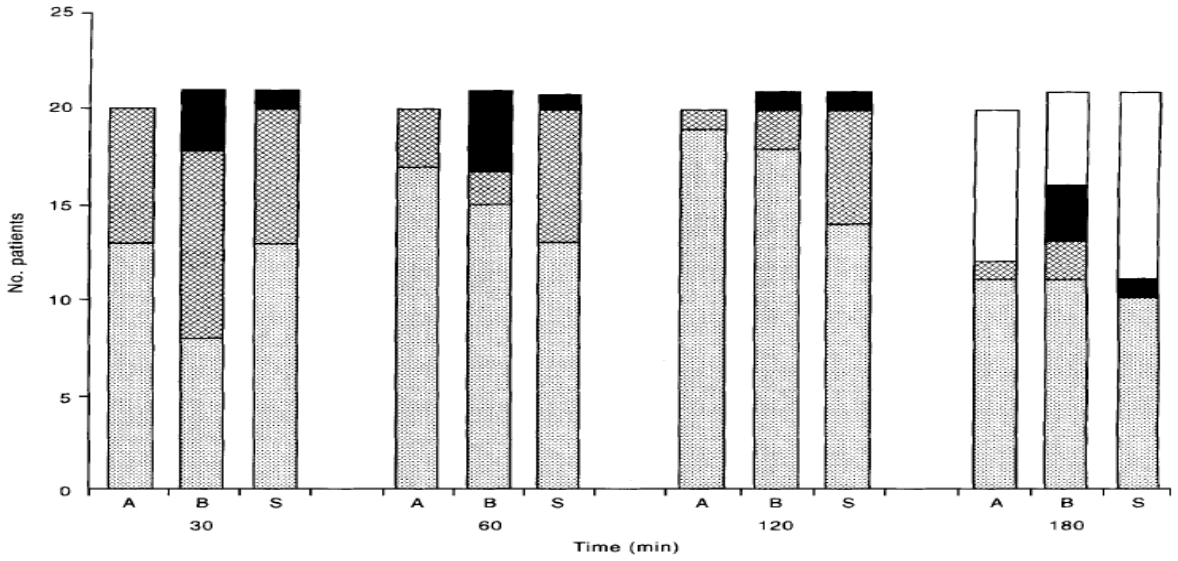



Figure 3. Mild pain (▨; pain score of 0 or 1) compared with severe pain (▩; pain score of 2 or 3) following either topical amethocaine (A), sub-conjunctival bupivacaine (B) or topical normal saline (S). (Using Chi-squared analysis and excluding patients who were 'not recorded' (■) or 'discharged' (□). Comparing pain scores between the three treatments: at 30 min $P = 0.34$; at 60 min $P = 0.16$; at 120 min $P = 0.06$; at 180 min $P = 0.43$.)

### 5.1.5 Kim el al (2003): Amethocaine or ketorolac eyedrops provide inadequate analgesia in pediatric strabismus surgery

This study was a prospective randomized, double-blind placebo controlled clinical trial. The study compared the effect of placebo to intraoperative 0.5% topical amethocaine or 0.5% topical ketorolac on pain control after strabismus surgery in children. In this study, a total of 51 healthy children between the ages of two and seven years who were undergoing elective bilateral recession surgery were randomized to receive either amethocaine (19 subjects) or ketorolac (14 subjects) or placebo (18 subjects). Two drops of the study medication were placed in each eye at the start and end of the surgery. Pain was assessed with a modified children's hospital of eastern Ontario pain scores (CHEOPS). According to the authors, CHEOPS is a behavioral scale intended for children ages 1 through 7 which contains six indicators (cry, facial, verbal, torso, touch, legs). Each behavioral indicator is scored with 1 or 2 except "cry", "facial" and "verbal". Cry is scored using a 1, 2 or 3. Facial and verbal are scored using a 0, 1 or 2 (Table 8). The minimum score for a given patient is 4 and the maximum score is 13.

As can be seen in Table 9, there was no statistically significant difference in selected baseline demographic characteristics (age sex and weight) among the three treatment groups. The study also reported that there was no statistically significance difference in pain scores between the three groups. The reported median (range) pain scores were 5(4-7), 5(5-9), and 5 (4-8) in the placebo, ketorolac and amethocaine groups respectively (Table 10). Because no variability

measure was provided, the reviewer was unable to provide interval estimates for the treatment differences. It is stated in the study that, patients with a pain score greater than 6 were given oral acetaminophen. If the oral acetaminophen does not alleviate the pain, codeine was chosen as a second line analgesic at a dose of 1.0 mg·kg–1. The study reported that overall 43% of children required acetaminophen postoperatively and this was distributed equally amongst the three groups. No summary data is provided for this. The publication concluded that the study did not demonstrate a beneficial effect of topical ketorolac or amethocaine versus placebo for pain control in children undergoing strabismus surgery.

**Table 8: Modified children's hospital of eastern Ontario pain scores (Kim 2003)**

| Item | Behavior | Score |
|---|---|---|
| Cry | No cry | 1 |
| | Moan/ Crying | 2 |
| | Smiling/ Positive | 3 |
| Facial Expression | Neutral | 0 |
| | Grimace | 1 |
| Verbal Expression | Positive Statement | 2 |
| | Non-eye pain related complaint or silence | 1 |
| | Pain complaint related to eye surgery | 2 |
| Torso | Body at rest | 1 |
| | Moving | 2 |
| Touching | Does not touch eyes | 1 |
| | Rubs eyes persistently | 2 |
| Legs | Relaxed or gently Moving | 1 |
| | Restless/drawn up/tense/resisting/restrained | 2 |

Minimum score=4, maximum score=13

**Table 9 : Patient demographics (Kim 2003)**

| | Treatment | | |
|---|---|---|---|
| | Ketrolac N=14 | Placebo N=18 | Amethocaine N=19 |
| Age | 4.7±2.6 | 4.4±1.6 | 4.8±1.9 |
| Weight (Kg) | 19.3±8.4 | 18.5±4.7 | 18.0±3.0 |
| Sex (M:F) | 4:10 | 8:10 | 7:12 |

**Table 10: Anesthetic data summary (Kim 2003)**

| | Treatment | | |
|---|---|---|---|
| | Ketrolac N=14 | Placebo N=18 | Amethocaine N=19 |
| CHEOPs | 5 (4-8) | 5 (4-9) | 5 (4-8) |
| Premedication (midazolam) | 8/14 | 10/18 | 6/19 |
| Induction (iv; inhal) | 5:9 | 2:16 | 9:10 |
| Halothane (maint. %) | 1.6±0.4 | 1.4±0.4 | 1.4±0.6 |
| $N_2O$ (maint. %) | 66±5 | 61±6 | 68±3 |

| | | | |
|---|---|---|---|
| Iv fluids (mL) | 204±173 | 294±186 | 214+167 |
| PARR fluids (mL) | 47±31 | 60±40 | 56±40 |
| Anesthesia time (min) | 59±6 | 57±13 | 60±12 |
| PARA time (min) | 45±16 | 44±13 | 45±13 |
| SDCU time (min) | 80±19 | 82±24 | 80±20 |

CHEOP=Children's Hospital of Eastern Ontario Pain Scores; PARR=post-anesthesia recovery room; SDCU=Surgical day care unit. Note all figures are mean ±SD

### 5.1.6 Rifkin et al (2012): Factors Affecting patient's pain intensity during in office Intravitreal injection procedure.

This is a prospective, randomized study which included 60 patients in a single center receiving at least 5 consecutive intravitreal injections for various conditions (diabetic macular edema, age-related macular degeneration, and central retinal vein occlusion). The main objective of this study was to determine factors that are associated with greatest patient comfort in intravitreal injection.

In this study, patients were randomized to 1 of 3 accepted and commonly used forms of anesthesia: TetraVisc (tetracaine HCl 0.5% gel; Cynacon/Ocusoft, Rosenberg, TX), proparacaine HCl (CompuMed, Inc, Los Angeles, CA), or tetracaine HCl ophthalmic solution (Alcon Surgical, Fort Worth, TX). A single drop of anesthetic was given 3 times over a 5-minute period and each patient received at least 5 consecutive injections at monthly intervals. For those patients who received more than five injections within the study period, only the first five were studied for pain analysis. All patients were naive to injection before enrollment, and the patients were balanced in terms of treated pathology; patients with macular degeneration, diabetic macular edema, and vein occlusion were distributed evenly among the treatment groups.

Fifteen minutes after treatment, patients were asked to rate their pain from 0 to 10 using a Visual Analog Pain score survey, where 0 = no pain/no distress and 10 = agonizing pain/unbearable distress. The publication states that the visual analog pain scale used in this study has been shown to be a reliable and reproducible method of measuring patient pain. The outcomes of the self-reported pain scores were recorded and stratified by age, gender, diagnosis, injected eye, injection number, substance injected, needle gauge, and perception of visual acuity improvement from previous injection.

Analysis of variance was used as the statistical analysis of choice to compare the three groups of anesthetics, substance injected, diagnosis, injection number, and needle gauge. Student's t-test was used to compare effect of perception of visual acuity measurement from previous injection on pain score, and gender, age, and injected eye. In this summary the focus will be on the comparison of the average pain score among the three anesthetics.

The publication reported that there was a statistically significant difference (P <0.01) between patients receiving different topical anesthesia before their intravitreal injection. It states that patients receiving tetracaine (Group 3) reported the lowest pain score of 3.05 + 2.01. Patients in Group 2 (TetraVisc) reported an average pain score of 3.17 + 2.18 and patients in Group 1 (proparacaine) reported the highest pain score, of 3.39 + 2.26 (Figure 4). Because pain outcomes were recorded for each of the 20 subjects after each of the five intravitreal injections, the total number of pain measurements per subject is 5. The average pain score for each group was thus based on 100 pain measurements.

In addition to comparing average pain score among the three anesthetics, the study also performed comparison of the average pain score by gender, age, improvement of visual acuity, treatments used for the underlining condition (Avastin, Lucentis), and the type of disease (AMD, DME, CRVO). The summary results are presented in Figure 5.

The results in this study should be interpreted with caution. Firstly, despite the statistical significance, the authors reported that a clinical significance is unlikely as the magnitude of difference between the groups was quite small. Secondly, it is not clear if the statistical analysis (ANOVA) in this study appropriately accounted for within-subject dependence due to multiple measurements per eye. Thirdly, even if we trust the reported p-value from the ANOVA model, it only provides evidence that there is a difference among the three treatments. This reviewer's pairwise comparison using the reported summary data (Mean± SD) did not show a statistical significant difference for any pair of treatments. The observed differences (95% CI) were: (-0.34; (-0.94, 0.26); tetracaine vs. proparacaine), (-0.12; (-0.70, 0.46); tetracaine vs. TetraVisc) and -0.22; (-0.84, 0.40); TetraVisc vs. proparacaine).

**Figure 4 : Comparison of average pain score among three anesthetics (Rifkin 2012)**

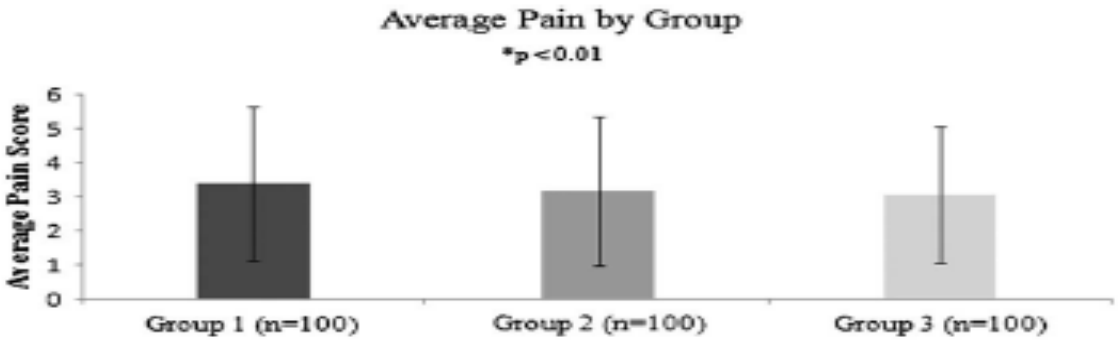



**Fig. 1.** Comparison of average pain scores of patients receiving proparacaine (Group 1), TetraVisc (Group 2), and tetracaine (Group 3) before injection. Analysis of variance detected a statistically significant difference between Group 3 and the other 2 groups.

**Figure 5 : Comparison of average pain score among subgroups made based on demographic and disease characteristics (Rifkin 2012)**

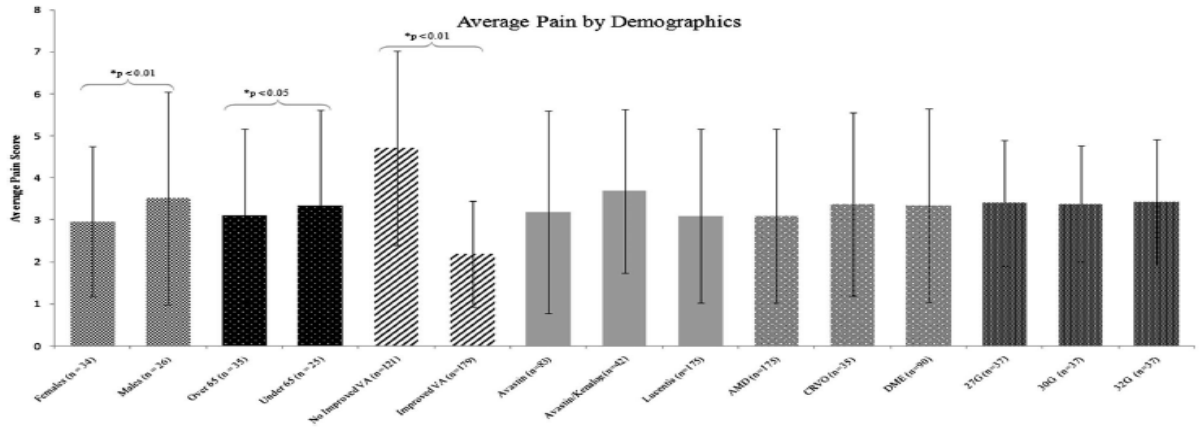



**Fig. 2.** Comparison of average pain scores of patients by demographics. Statistical significance was found with sex of the patient, age, perception of improvement of vision from previous injection and time of day of injection.

### 5.1.7 Moshirfar et al (2014): Prospective, randomized, contralateral eye comparison of tetracaine and proparacaine for pain control in laser in situ keratomileusis and photorefractive keratectomy

This study is prospective, single-masked, randomized study. The study is comprised of 256 eyes from 128 consecutive patients over the age of 21 who are being treated with LASIK or photorefractive keratectomy (PRK). These subjects were randomized to receive tetracaine in one eye and proparacaine in the other. The patients were blinded as to which anesthetic agent was used in each eye. Patient demographic and treatment summary is presented in Table 11.

Pain was the primary outcome variable, measured upon instillation of proparacaine or tetracaine intraoperatively, immediately postoperatively, 30 minutes postoperatively, overnight, and on postoperative day 1. Patients were asked to grade the degree of pain in each eye on a numeric pain rating scale according to severity (0= no pain, 5= moderate pain, 10= severe pain). Additionally, patients were asked 30 minutes after surgery which anesthetic agent they would choose.

The publication states that the study outcomes were modeled using multivariable mixed effects regression models, which permitted a paired comparison between eyes in the same patient, while controlling for covariates. Mixed effects linear regression was used for continuous outcomes, and mixed effects logistic regression was used for binary or dichotomous outcomes.

The average pain scores experienced at the various time points in the study are shown in Table 12. Upon drop instillation, patients perceived 2.1 points more pain in eyes treated with tetracaine than in eyes treated with proparacaine (95% CI: 1.8–2.5, P<0.001), after controlling

for baseline pain. Intraoperatively, patients perceived a marginally significant 0.4 points more pain in the eye treated with tetracaine than in the eye treated with proparacaine (95% CI 0.0–0.8, P=0.067), after controlling for pain experienced during drop instillation. Immediately following surgery, patients discerned a non-significant (0.1 point) increase in pain perception in the eye treated with proparacaine relative to the eye treated with tetracaine (95% CI -0.2, 0.3, P=0.58), after controlling for pain experienced during surgery.

At 30 minutes postoperatively, there was a distinction between patients who underwent LASIK surgery rather than PRK surgery. The PRK patients did not perceive a difference in pain control between proparacaine and tetracaine (0.1 points difference, 95% CI -0.2, 0.5, P=0.53; Figure 6). The LASIK patients, however, perceived 1.5 points greater pain in the eye treated with proparacaine as opposed to the eye treated with tetracaine (95% CI 1.0–2.0, P<0.001; Figure 7). No differences in pain were seen overnight or one day after the procedure.

In summary, both anesthetic agents resulted in diminished amounts of subjective pain in patients undergoing LASIK and PRK. Tetracaine caused significantly more pain upon instillation than proparacaine for both LASIK and PRK patients. However, LASIK patients noted significantly less pain 30 minutes after surgery when treated with tetracaine. Significantly more LASIK patients preferred the eye treated with tetracaine. These differences were not present in the PRK group. Based on these findings, the authors concluded that both tetracaine and proparacaine are effective methods of topical anesthesia in LASIK and PRK. However, tetracaine resulted in greater analgesia 30 minutes after surgery in the LASIK group and patients in the LASIK group expressed a preference for tetracaine over proparacaine. There was no significant drop preference among PRK patients.

**Table 11 : Patient demographics and treatment summary (Moshirfar 2014)**

| | LASIK (n=67 patients; n=134 eyes) | PRK (n=61 patients; n=122 eyes) | Combined sample (n=128 patients; n=256 eyes) |
|---|---|---|---|
| Patient age, years | | | |
| Mean ± SD (range) | 33.5±7.1 (21–52) | 32.1±6.9 (21–55) | 32.8±7.0 (21–55) |
| Sex, n (%) | | | |
| Male | 28 (42) | 29 (48) | 57 (45) |
| Female | 39 (58) | 32 (52) | 71 (55) |
| Preoperative spherical equivalent | | | |
| Mean ± SD | –3.80±1.93 | –3.81±1.69 | –3.81±1.81 |
| Laser used, n (%) | | | |
| Allegretto | 48 (72) | 29 (48) | 77 (60) |
| Visx | 19 (28) | 32 (52) | 51 (40) |
| Order of operation, n (%) | | | |
| Proparacaine eye first | 35 (52) | 36 (59) | 71 (55) |
| Tetracaine eye first | 32 (48) | 25 (41) | 57 (45) |

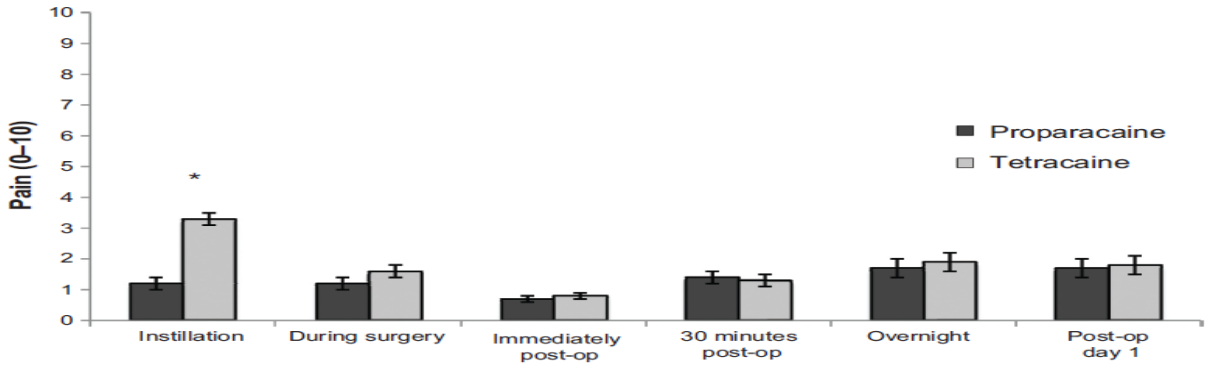
**Abbreviations:** LASIK, laser in situ keratomileusis; PRK, photorefractive keratectomy; SD, standard deviation.

## Table 12 : Pain outcome summary (Moshirfar 2014)

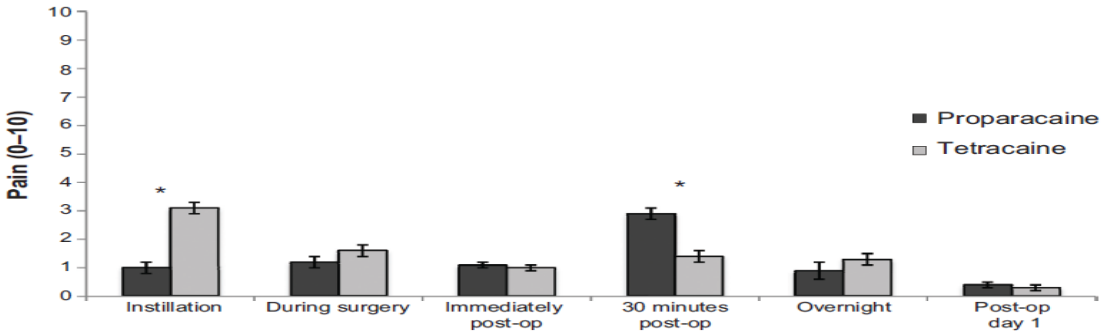
| Time point | Proparacaine pain adjusted mean ± SE | Tetracaine pain adjusted mean ± SE | Adjusted mean difference (P-T)* (95% CI) | *P*-value |
|---|---|---|---|---|
| Total sample (n=128 patients) | | | | |
| Instillation | 1.1±0.2 | 3.2±0.2 | −2.1 (−2.5, −1.8) | <0.001 |
| During surgery | 1.2±0.2 | 1.6±0.2 | −0.4 (−0.8, 0.0) | 0.067 |
| Immediately postoperatively | 0.9±0.1 | 0.9±0.1 | 0.1 (−0.2, 0.3) | 0.60 |
| 30 minutes postoperatively | 2.2±0.1 | 1.3±0.1 | 0.8 (0.5, 1.2) | <0.001 |
| Overnight | 1.3±0.2 | 1.6±0.2 | −0.3 (−0.6, 0.2) | 0.23 |
| Postoperative day 1 | 1.0±0.2 | 1.0±0.2 | 0.0 (−0.2, 0.3) | 0.89 |
| LASIK (n=67 patients) | | | | |
| Instillation | 1.0±0.2 | 3.1±0.2 | −2.1 (−2.5, −1.6) | <0.001 |
| During surgery | 1.2±0.2 | 1.6±0.2 | −0.4 (−1.1, 0.2) | 0.22 |
| Immediately postoperatively | 1.1±0.1 | 1.0±0.1 | 0.1 (−0.2, 0.5) | 0.48 |
| 30 minutes postoperatively | 2.9±0.2 | 1.4±0.2 | 1.5 (1.0, 2.0) | <0.001 |
| Overnight | 0.9±0.3 | 1.3±0.2 | −0.4 (−1.1, 0.2) | 0.15 |
| Postoperative day 1 | 0.4±0.1 | 0.3±0.1 | 0.1 (−0.2, 0.3) | 0.53 |
| PRK (n=61 patients) | | | | |
| Instillation | 1.2±0.2 | 3.3±0.2 | −2.2 (−2.7, −1.6) | <0.001 |
| During surgery | 1.2±0.2 | 1.6±0.2 | −0.4 (−1.1, 0.2) | 0.12 |
| Immediately postoperatively | 0.7±0.1 | 0.8±0.1 | 0.0 (−0.3, 0.2) | 0.92 |
| 30 minutes postoperatively | 1.4±0.2 | 1.3±0.2 | 0.1 (−0.2, 0.5) | 0.53 |
| Overnight | 1.7±0.3 | 1.9±0.3 | −0.2 (−0.7, 0.4) | 0.52 |
| Postoperative day 1 | 1.7±0.3 | 1.8±0.3 | 0.0 (−0.5, 0.5) | 0.90 |

**Notes:** *Adjusted for pain at previous measurement time using a multivariable mixed effects linear regression model; after instillation, also adjusted for surgical procedure (LASIK or PRK).
**Abbreviations:** LASIK, laser in situ keratomileusis; PRK, photorefractive keratectomy; P, proparacaine; T, tetracaine; SE, standard error of the mean; CI, confidence interval.

## Figure 6 : Pain outcomes for photorefractive keratectomy (PKR) (Moshirfar 2014)




## Figure 7 : Pain outcomes for LASIK (Moshirfar 2014)



### 5.1.8 Chalam et al. (2009): Comparative efficacy of topical tetraVisc versus lidocaine gel in cataract surgery

This was a randomized, multi-surgeon, controlled clinical trial. In this study, 122 eyes of 122 patients were operated for cataract in the study: 61 patients were randomly assigned to receive five doses of lidocaine 2% gel or tetracaine solution 0.5% (TetraVisc, 0.5 ml) every 5 minutes 20 minutes before clear corneal phacoemulsification. Both the patient and the independent observer were masked to the anesthesia used. In tetracaine group there were 25 males and 36 females and in lidocaine group there were 28 males and 33 females. There was no statistically significant difference in the mean age of subjects between the tetracaine group (70.4 ± 4.1; (mean ± SD) years and in the lidocaine group was (70.6 ± 10.5; mean ± SD) years (p=0.89).

The main outcome measure was visual analog scale (0 to 10) recorded by the patients within 10 minutes of completion of surgery. This outcome was used to measure intra-operative pain. Secondary outcome measures included patients' discomfort due to tissue manipulation and surgeon graded patients' cooperation. Duration of surgery and intra-operative complications were also recorded.

The results of the study are summarized in Table 13. Intraoperative pain scores by VAS were 0.7 ± 0.31 (mean + SD) in the tetracaine group and 1.8 ± 0.4 (mean + SD) in the lidocaine group. This difference was statistically significant (P <0.001). Patient cooperation, as graded by the surgeon, was 8.3 ± 0.3 (mean ± SD) in tetracaine group and 8.4 ± 0.6 (mean ± SD) in the lidocaine group (p = 0.25). Intraoperative corneal clarity was good in 59 of 61 patients (97%) in the tetracaine group and in 55 of 61 patients (90%) in the lidocaine group (p = 0.16). The mean duration of surgery was 13.1 ± 2.7 minutes overall with mean of 13.4 ± 2.3, 12.4 ± 3.4 and 13.7 ± 2.1 minutes for the 3 surgeons who were involved in the study (p = 0.07). Mean VAS scores for the 3 surgeons were 8.20 ± 0.5, 8.1 ± 0.4 and 8.3 ± 0.4 respectively (p = 0.12). Based on the above findings, the authors concluded that topical TetraVisc solution was superior to lidocaine 2% gel for pain control in patients undergoing clear corneal phacoemulsification. Lidocaine 2% gel is similar to TetraVisc in patient comfort and surgeon satisfaction.

**Table 13 : Patient characteristics and anesthetic efficacy summary (Chalam 2009)**

| | Treatment | | | |
|---|---|---|---|---|
| | TetraVisc N=61 | Lidocaine N=61 | Diff (95% CI) | P-value |
| Age in years (Mean ± SD) | 70.4±4.1 | 70.6±10.5 | | 0.980 |
| Visual analog pain scores (Mean ± SD) | 0.7±0.31 | 1.8±0.4 | -1.1 (-1.21, -0.98) | <0.001 |
| Patient cooperation (Mean ± SD) | 8.3±0.3 | 8.4±0.6 | | 0.240 |
| Clear corneal clarity (n (%)) | 59 (97.0%) | 55 (90.0%) | | 0.160 |
| Intra-operative complications (n (%)) | 1 (1.6%) | 3 (4.8%) | | 0.220 |

### 5.1.9 Shafi et al. (1998): Randomised prospective masked study comparing patient comfort following the instillation of topical proxymetacaine and amethocaine

This was a randomized, masked, double blind, prospective study. The study involved a sample of 53 consecutive patients (17 Male and 36 females) with a mean age of 64.7 years attending the ophthalmic outpatient department requiring tonometry.

In this study, each patient received one drop of amethocaine 0.5% in one eye and one drop of and proxymetacaine 0.5% in the other eye. For each subject, the duration of the stinging sensation immediately after the instillation of the respective treatment was measured. The severity of discomfort following the eye drops was assessed using both a descriptive method and a linear analogue method. In the descriptive method, patients assigned the sensation of discomfort into categories: “no pain”, “mild pain”, “moderate pain”, “severe pain”, and “very severe pain”. These five categories were arbitrarily scored from 0 to 4 respectively. This was followed by assessments using a 100 mm unmarked linear analogue discomfort scale. Subjects were asked to score the severity of their discomfort on the linear analogue scale ranging from “no pain” to “very severe pain”.

Patients’ preference of either drop or lack of preference was noted. To confirm the proper instillation of the anesthetic agents, scheduled tonometry using a Tonopen was performed 5 minutes after drop instillation, providing evidence of satisfactory anesthetic effect. Tonometry was regarded as a success if it was easily performed and without patient discomfort. Tonometry was regarded as unsuccessful if the patient felt uncomfortable.

The percentage of subjects experiencing “no pain”, “mild pain”, “moderate pain”, “severe pain”, and “very severe pain” on the descriptive discomfort scale for eyes receiving amethocaine and proxymetacaine is presented in Figure 8. The difference and the corresponding 95% CI for the difference in the proportion of subjects with no pain (amethocaine-proxymetacaine) was computed assuming independence of measurements coming from the same subject was -67% (-80.7%, -53.2%).

Using the wilcoxon rank sum test, the authors reported that there was a statistically significant difference in the mean descriptive discomfort score between proxymetacaine and for amethocaine (14.2 vs. 2.6; p= 0.01). There was also a statistically significance difference (p <0.001) in the mean duration of stinging between proxymetacaine (3.2 seconds (SD 6.3)) and amethocaine (22.1 seconds (SD 10.7)).

The distribution of discomfort along the unmarked linear analogue scale of length 100 mm for eyes receiving amethocaine and proxymetacaine is presented in Figure 9. Based on a t-test, the authors reported that there was a statistically significant difference in the mean linear analogue score between proxymetacaine and amethocaine (5.8 (0.9) vs, 35.6 (2.6); p<0.001).

Eighty-nine per cent of patients (n=47) preferred proxymetacaine while only one patient preferred amethocaine. Nine per cent (n=5) felt that there was no difference in either using proxymetacaine or amethocaine. There was no statistically significant difference between proxymetacaine and amethocaine in the success of tonometry rate (93% vs 98%; diff (95% CI): 5.0% (-2.8%, 12.8%); p=0.08). Based on the above findings, the authors concluded that proxymetacaine is more comfortable on installation than amethocaine.

**Figure 8 : Pain summary (Shafi 1998)**

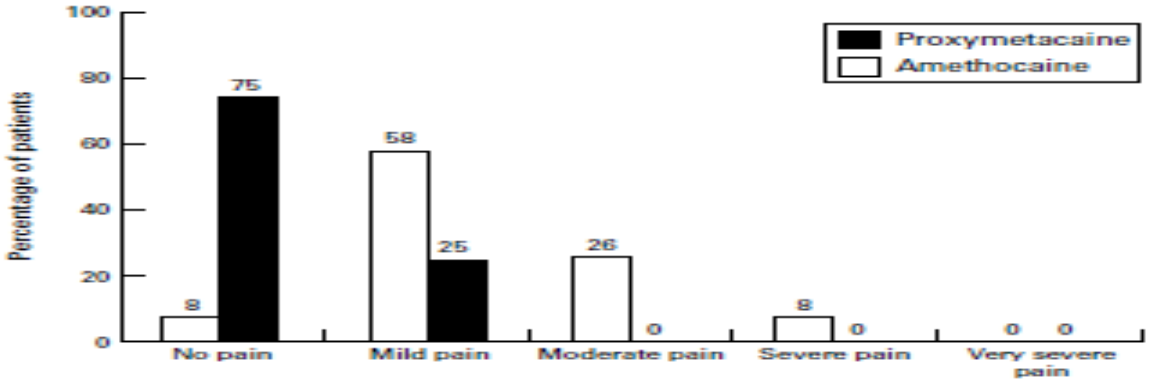
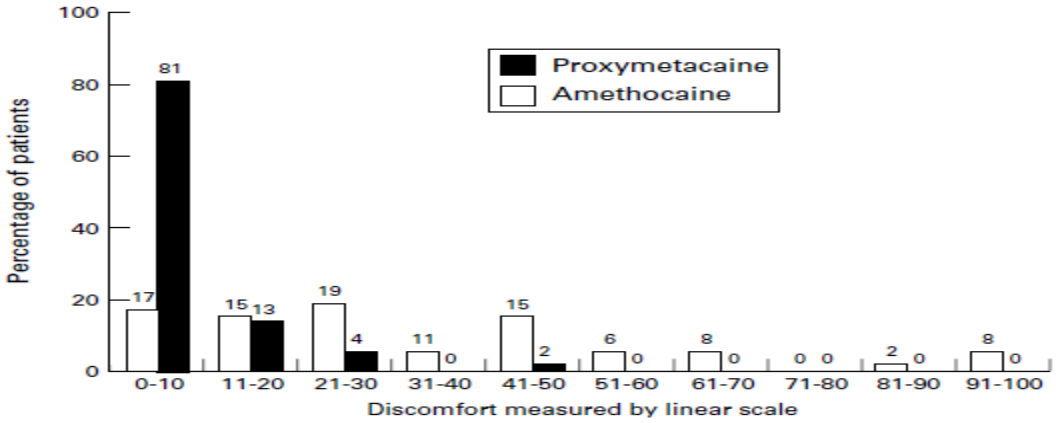



**Figure 9 : Summary of discomfort measured by linear scale (Shafi 1998)**




### 5.1.10 <u>Yau et al (2011): Intravitreal Injection Anesthesia—Comparison of Different Topical Agents: A Prospective Randomized Controlled Trial</u>

This is a randomized, triple-armed, double-blinded, prospective, single-centered trial in patients receiving intravitreal ranibizumab for neovascular age-related macular degeneration. In this study, 93 patients 50 years of age or older were randomized 1:1:1 to receive 0.5% tetracaine

hydrochloride drops and a 4% lidocaine pledget (n =31), 0.5% tetracaine hydrochloride drops alone (n =31), or 4% cocaine (epinephrine 1/100 000) drops alone (n =31).

The authors state that their sample size was calculated to detect a 13-point difference, with the level of significance set at a two-sided 5% and a power of 80%. A standard deviation (SD) of 16 was set as a compromise between similar prior studies, clinical judgment, and feasibility of the sample size. A Bonferroni adjustment was made to account for the comparison of 3 means. Using the above parameters, the sample size was determined to be 31 per group, with a total of 93 subjects.

One to two drops of topical anesthetic for each patient. Immediately following the injection, a study coordinator explained the 100-mm visual analogue scale (VAS) for pain and asked the subject to plot the level of pain he or she experienced specifically during the moment of injection. Per the authors, the VAS scale is the methodology that is most commonly used for the evaluation of pain severity and relief and has been employed in similar studies measuring ocular comfort. Those who could not adequately visualize the scale were prompted to vocalize a number from 0 to 100. Subjects were asked the same questionnaire 15 minutes later, without visualization of their first rating. A separate pain scale was employed to record physician-perceived pain. Per the authors, the Wong-Baker FACES scale was chosen primarily for its ease of use. The primary outcome of this study was the average of the 2 VAS pain scores. The secondary outcome was the physician-perceived pain score.

Demographic and procedural characteristics among groups were compared using descriptive statistics and univariate analysis as appropriate. One-way analysis of variance was used to compare the primary and secondary outcomes among treatment groups. Log transformation was applied to normalize data.

The summary shows that a total of 97 patients satisfied the inclusion criteria, with 93 consenting to participate in the trial. There were no deviations from protocol. All subjects allocated to a treatment group were included in the analysis. No adverse events were reported during or immediately after the intervention. The 3 specialists performing the injections were evenly distributed among the groups, as were the anesthetic operators. Baseline characteristics for each treatment group are described in Table 5.

The article reported that there was no significant difference (P=0 .549) between groups for average VAS pain score. Similarly, there was no significant difference (P =0.790) in the physician-perceived pain score between groups. There was also no significant difference between the average VAS and Wong-Baker FACES score for each treatment group (Table 15).

The Means VAS pain score for 0.5% tetracaine hydrochloride + 4% lidocaine pledget, 0.5% tetracaine hydrochloride drops alone and 4% cocaine (epinephrine 1/100 000) drops were respectively: 19 (95% confidence interval [CI] 12–26), 21 (95% CI 13–29), and 21 (95% CI 16–

27) respectively. Mean Wong-Baker pain scores for 0.5% tetracaine hydrochloride + 4% lidocaine pledget, 0.5% tetracaine hydrochloride drops alone and 4% cocaine (epinephrine 1/100 000) drops respectively were 1.9 (95% CI 1.3–2.6), 2.1 (95% CI 1.4 –2.7), and 2.3 (95% CI 1.6 –3.1) respectively (Table 15).

**Table 14: Patient demographics (Yau 2011)**

| Characteristics | Treatment | | | P-value |
|---|---|---|---|---|
| | Tetracaine +Lidocaine 4% N=31 | Tetracaine N=31 | Cocaine 4% N=31 | |
| Age (year)* | 83.6±6 | 79.5±9.9 | 82.1±7.7 | 0.124[a] |
| Previous Injection | 6.1±4.6 | 5.6±4.4 | 6.1±6.2 | 0.895[a] |
| Male Number (%) | 10 (32%) | 15 (48%) | 12 (39%) | 0.430[b] |

*Data are presented as mean +SD; [a]1-way ANOVA test; [b] Kruskal-Wallis test

**Table 15: Comparison of Average pain score among three Anesthetics (Yau 2011)**

| Measure | Treatment | | | P-value[a] |
|---|---|---|---|---|
| | Tetracaine + Lidocaine 4% | Tetracaine | Cocaine 4% | |
| VAS | 19±20 | 21±21 | 21±16 | 0.549 |
| Wong-Baker | 1.9±1.8 | 2.1±1.8 | 2.3±2.0 | 0.790 |

*Data are presented as mean +SD; [a]1-way ANOVA with log transformation for normalization

### 5.1.11 Tsoumani et al (2010): Tetracaine 0.5% eye drops with or without lidocaine gel 2% in topical anesthesia for cataract surgery

This was a prospective, randomized, controlled study. This study included 51 patients aged between 51-86 years who were undergoing phacoemulsification under topical anesthesia. Eligible subjects were randomized into two groups to receive either tetracaine eye drops (24 (47%)) or combined tetracaine eye drops and lidocaine gel (27 (53%)).

Preoperatively, all patients were asked to answer a questionnaire to collect information about factors which could influence the evaluation of pain. Patients were also asked to grade their pain intraoperative (immediately after surgery) and postoperative (one hour after surgery) on a visual analog scale (VAS: VAS1 for intraoperative and VAS2 for postoperative). The scale ranges from 0 to 10; with 0 = no pain, 10 = severe unbearable pain. The patients were also asked to differentiate the characteristics of pain or discomfort. Data recorded included eye conditions and systemic diseases, age, gender, and whether the patient was escorted to the hospital by friends and relatives. The Student's t-test was used to compare the groups for statistical purposes. The summary results for the pain scores are presented in Table 16.

The study reported that there were no statistically significant differences between the treatment groups regarding patient age, education level, eye conditions, systemic diseases, and habitual use of analgesics. There was also no statistically significant difference between the two

treatment groups in the mean intraoperative and postoperative pain score. The authors concluded that both tetracaine 0.5% eye drops alone and the combination of tetracaine 0.5% eye drops plus lidocaine 2% gel have good anesthetic properties for topical use in cataract surgery.

**Table 16 : Summary pain scores (Tsoumani 2010)**

| | Anesthesia | N | Mean (SD) | P-values |
|---|---|---|---|---|
| Intraoperative pain | Tetracaine | 27 | 4.19 (2.321) | 0.663 |
| | Tetracaine+lidocaine gel | 24 | 3.88 (2.724) | |
| | | | | |
| postoperative pain | Tetracaine | 27 | 1.11 (1.625) | 0.312 |
| | Tetracaine+lidocaine gel | 24 | 1.58 (1.666) | |

### 5.1.12 Sanabria (2013): Ocular Pain After Intravitreal Injection

This is a perspective randomized, double-masked, single-center trial in patients undergoing intravitreal injections. In this study, 156 patients were randomized in a 1:1 ratio to receive tetracaine plus naphazoline (n =86), or lidocaine (n =70). Subjects randomized to the tetracaine plus arm received one anesthetic drop containing 0.5% tetracaine and 0.05% naphazoline (commercialized as ophthalmic topical anesthetic) 10 min before the IVI. The instillation was repeated 1 minute, 5 and 6 minutes later. Subjects in the lidocaine arm received a commercially available local anesthetic (5% lidocaine) that can be used in ophthalmic topical anesthesia with the same time intervals.

Main outcome measures were the amount of pain, the presence of conjunctival hemorrhage, intraocular pressure (IOP) and the presence of vitreous reflux. A numerical score evaluated pain immediately after the injection, 30 min and 24 h later. Demographic characteristics were summarized using descriptive statistics and a Mann-Whitney U test was used to compare groups with respect to other outcomes including pain. The summary of age and gender by treatment group are described in Table 17. The two groups are comparable with respect to baseline characteristic. In each group, there were more male participants than female and the average age was close 76 and 77 years in the tetracaine plus naphazoline and lidocaine groups respectively.

The summaries show that there was no significant difference in the mean pain score between the two treatment arms immediately after injection (P=0.727) and at 30 minutes post injection (P=0,210) and 24 hours after injection (P=0.979). The Mean (SD) pain scores for the tetracaine plus naphazoline arm were 2.85 (2.23), 2.00 (1.87) and 1.81 (2.23) immediately after injection, after 30 minutes and after 24 hours respectively. The corresponding values for the lidocaine arm were 2.67 (2.00), 1.58 (1.55) and 1.77 (2.09).

**Table 17: Patient demographics (Sanabria 2013)**

| Characteristics | Treatment | |
|---|---|---|
| | Tetracaine + naphazoline N=86 | Lidocaine N=31 |

| | | |
|---|---|---|
| Age (year)* | 76±13 | 77±12 |
| Sex: Male/female | 57/29 | 43/27 |

*Data are presented as mean +SD;

### 5.1.13 Lawrenson (1998): Comparison of tolerability and efficacy of unit-dose, preservative-free topical ocular anesthetics

The purpose of this study was to compare the tolerability, and the depth and duration of corneal anaesthesia following instillation of one drop of 0.4% oxybuprocaine (benoxinate), 0.5% amethocaine, or 0.5% proxymetacaine. In this study, 14 healthy subjects between the ages of 18 and 40 years (mean age 26 years) with no history of ocular disease were enrolled.

Each subject attended two sessions, and on each occasion the baseline sensitivity was recorded for each eye. At each session, 35 ml (measured using a micropipette) of one study preparation of one of the four treatments was instilled into the right eye, and 35 ml of a second study preparation was instilled into the left eye. The order of instillations was randomized. All instillations were performed by a third party to ensure double-masked conditions. The tolerability of each anaesthetic was assessed using a linear ten-point arbitrary comfort scale. Following instillation, sensitivity was measured at 1, 2, 5, 10, 15, 20, and 30 min, and every 5 min thereafter until the touch sensitivity was restored to its baseline value. The procedure was then repeated for the second eye. Total anaesthesia was recorded when the subject was unaware of any touch sensation following corneal contact with a 1 cm length of the 0.12 mm diameter. Corneal sensitivity was measured using a slit-lamp mounted Cochet-Bonnet aesthesiometer.

Per the authors, the proportion of subjects achieving total anaesthesia for each drug was compared at each time point using McNemar's test. There was no significant difference between the topical ocular anaesthetic drugs for the percentage of subjects achieving total anaesthesia at any time point. By 20 min after instillation, two subjects still showed total anaesthesia with amethocaine, and one of these subjects also had total anaesthesia with proxymetacaine at 20 min. By 30 min, recovery had begun in all subjects, and recovery to baseline was complete in all but four cases, one for oxybuprocaine, one for amethocaine, and two for proxymetacaine, all of whom returned to baseline by 45 min (Figure 21).

The authors also stated that, the average times for onset of recovery ranged from 8 to 23 min, while for the return to baseline sensitivity the times ranged from 18 to 32 min. They reported that there was considerable inter-subject variation among this small population in both the duration of total anaesthesia and in the time taken for a return to baseline sensitivity. The mean baseline threshold sensitivity for the 14 subjects was 5.9 cm (SD 0.3 cm) (Figure 3). Tolerability data was analysed using the Wilcoxon Signed Ranks test. The results show that proxymetacaine was significantly better tolerated than either amethocaine ($P<0.01$) or oxybuprocaine ($P<0.0001$). The authors also reported that there was no significant difference in tolerability between oxybuprocaine and amethocaine. Based on these results, the authors concluded that, there seems little to choose clinically between the three active agents as regards

to clinical effectiveness. Proxymetacaine was significantly better tolerated than either amethocaine or oxybuprocaine.

**Figure 10 : Percent of subjects achieving total anesthesia (Lawrenson 1998)**

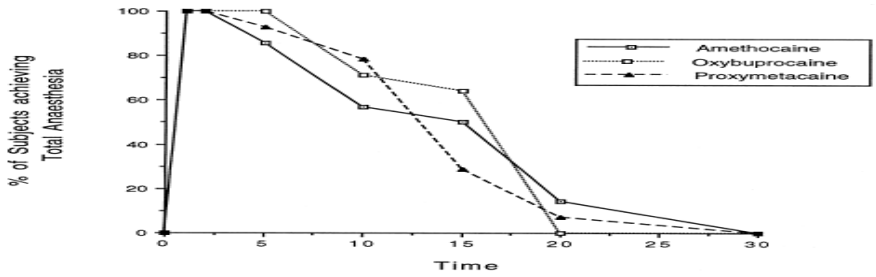



**Figure 11 : Average time in minutes for the onset and sensitivity to return to baseline (Lawrenson 1998)**

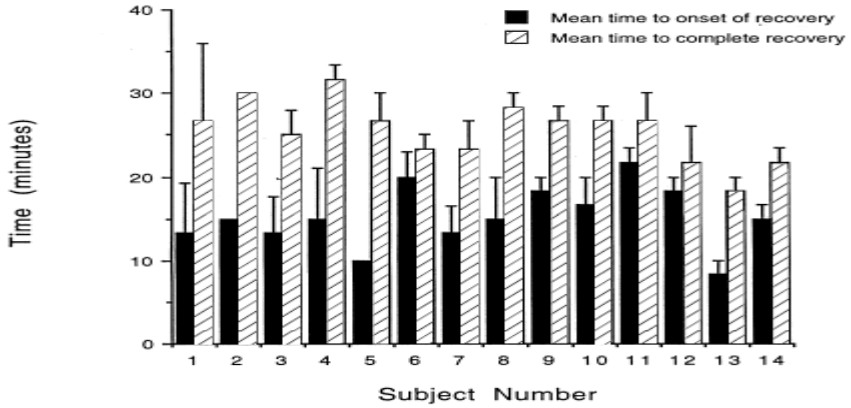
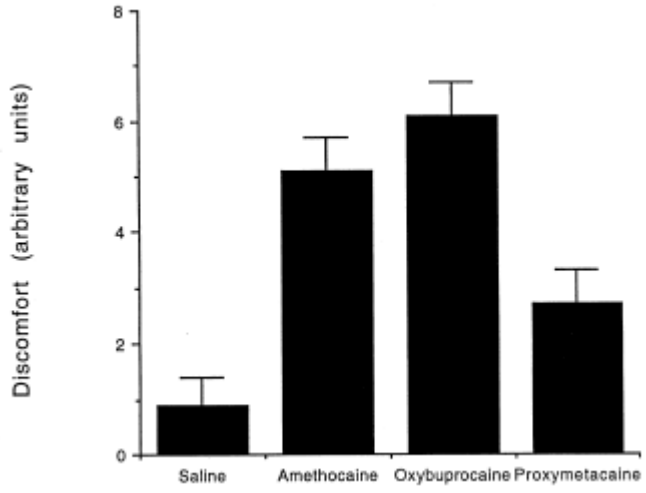



**Figure 12 : Average discomfort rating (Lawrenson 1998)**



### 5.1.14 Nomura (2001): Comparison of tolerability and efficacy of unit-dose, preservative-free topical ocular anesthetics

The purpose of this study was to compare the topical effects of tetracaine, lidocaine, and bupivacaine on corneal sensitivity in normal eyes. In this study, seventeen healthy volunteers (10 women and 7 men) with average age of 36.5 years were randomized into five groups: Group 1 0.5% tetracaine (n=6); group 2, 4% lidocaine (n =8); group 3, 0.75% bupivacaine (n =8); group 4, 0.5% tetracaine + 4% lidocaine (n =5); and group 5, 0.5% tetracaine + 0.75% bupivacaine (n=7).

Corneal sensitivity was measured using the Cochet-Bonnet anesthesiometer. The instrument consists of a cylinder encasing a 0.12-mm diameter nylon filament, the length of which can be varied from 6.0 to 0.5 cm. The lengths correspond to pressures of 11 to 200 $mg/mm^2$ when touched against the cornea, thus allowing quantification of corneal sensitivity stimulus.

The baseline corneal sensation (before instillation) of the study subjects were the same, which was 6.0 cm. Every 2.5 minutes after instillation, the cornea was touched by using Cochet-Bonnet anesthesiometer from 0.5 cm. Corneal sensitivity was measured in both eyes 1 minute before and at 2.5-minute intervals after the instillation of two-drop doses of topical anesthesia from a 23-gauge hypodermic needle, until baseline. Statistical analysis was performed using the Mann-Whitney test to compare characteristics of the five study groups. To evaluate differences between the absence of sensation of the five groups, statistical analysis was performed using the Minitab statistical package. The null hypothesis was rejected if the p-value was less than 0.005.

The results of the study show that, there was statistically significant difference between 4% lidocaine and 0.75% bupivacaine and 0.5% tetracaine + 0.75% bupivacaine ($P<0.0005$) with 4% lidocaine having a better effect (Figure 21). There was also a significant difference between 0.75% bupivacaine and 0.5% tetracaine + 4% lidocaine ($p < 0.005$). In this comparison, 0.5% tetracaine + 4% lidocaine had a better anesthetic effect (Figure 21). At 5.0 minutes after application, there was significant difference between 4% lidocaine and 0.75% bupivacaine ($p < 0.005$). 4% lidocaine had a better anesthetic effect than 0.75% bupivacaine (Figure 14). At 10.0 minutes after application, there was significant difference between 4% lidocaine and 0.5% tetracaine, 0.75% bupivacaine, and 0.5% tetracaine + 0.75% bupivacaine ($P<0.005$); with 4% lidocaine having a better anesthetic effect than any of the other three groups (Figure 15). The time course of corneal sensation, showed no difference between 0.5% tetracaine and 0.5% tetracaine + 0.75% bupivacaine, 4% lidocaine and 0.5% tetracaine + 4% lidocaine (Figure 16).

**Figure 13 : Mean (SD) corneal sensitivity 2.5 minutes post-injection (Nomura 2001)**

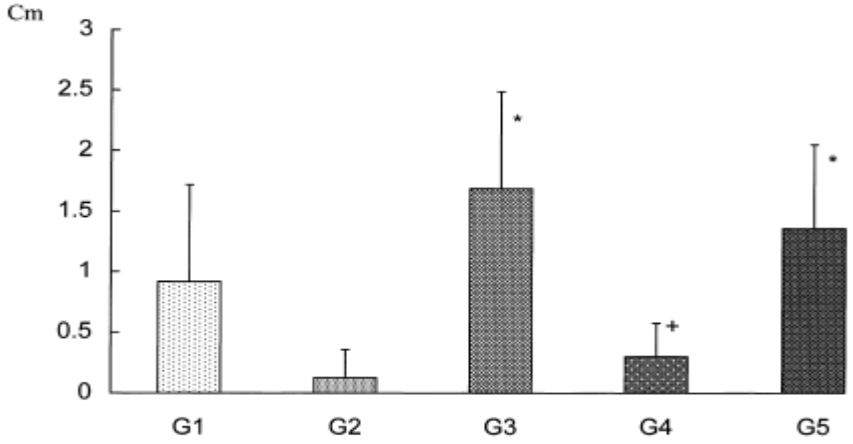



**Figure 14 : Mean (SD) corneal sensitivity 5 minutes post-injection (Nomura 2001)**

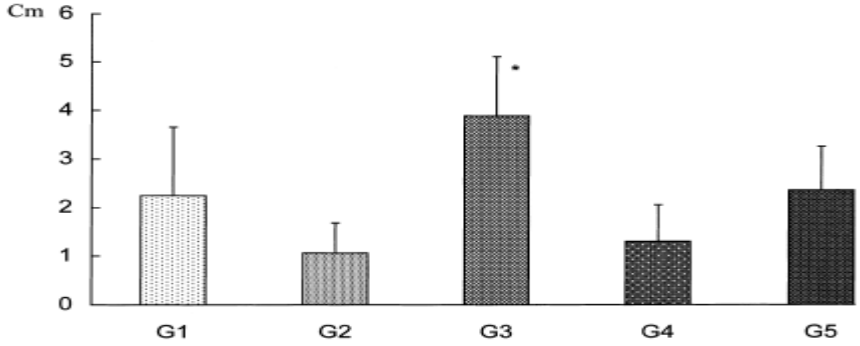



**Figure 15 : Mean (SD) corneal sensitivity 10 minutes post-injection (Nomura 2001)**

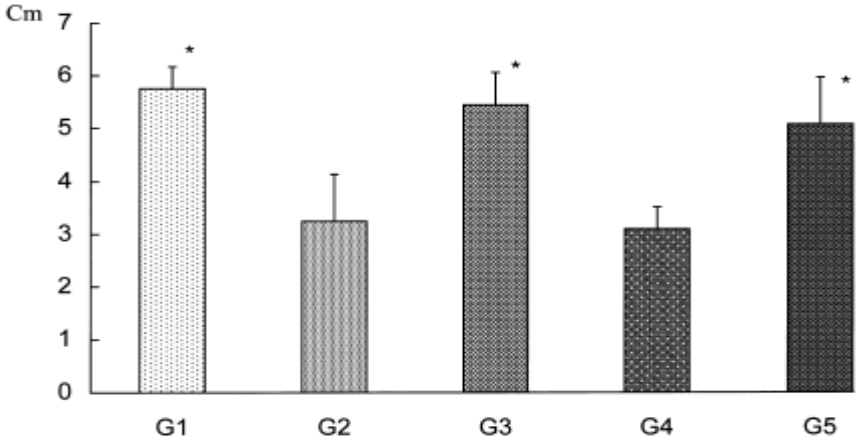
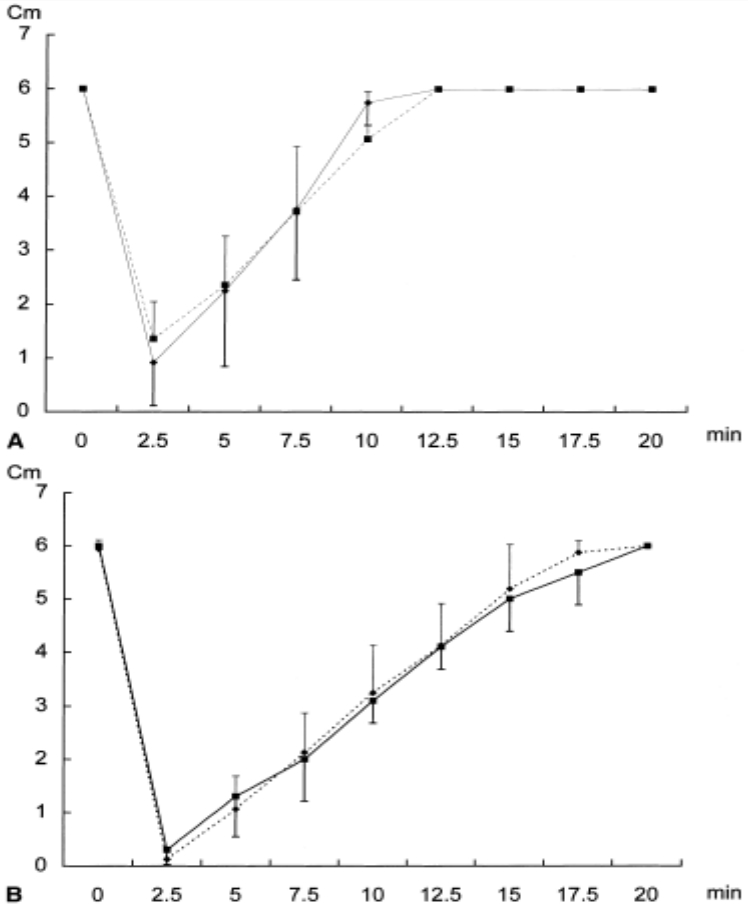


**Figure 16 : Time course of corneal sensation (Nomura 2001)**




There is no difference between group 1 (G1) and group 5 (G5). **B:** Time course of corneal sensation. There is no difference between group 2 (G2) and group 4 (G4). Mean ± SD are shown in the graphs.

### 5.1.15 Blaha et al. (2011): Randomized trial of Anesthetic methods for intravitreal injections

This study was a randomized, masked, controlled study to compare the effectiveness of 4 different anesthetic methods. The study enrolled 24 subjects (9 male, 15 females aged 67-93 years) requiring intravitreal injections. Subjects each received 4 intravitreal injections with each injection using one of 4 types of anesthesia (topical ocular proparacaine 0.5%, tetracaine 0.5%, lidocaine 4% and subconjunctival lidocaine 2%). Patients were masked to the schedule and type of anesthetic used at each visit. Immediately following the intravitreal injection, the patient filled out a grading sheet on the level of discomfort from both the anesthesia and the injection. A 0 to 10 pain scale representing no pain (0) to severe pain (10) (Figure 17) was used, and this was also read to the patient. The injector recorded any adverse outcomes from the anesthetic technique or the intravitreal injection.

**Figure 17 : Injection and anesthetic pain rating**

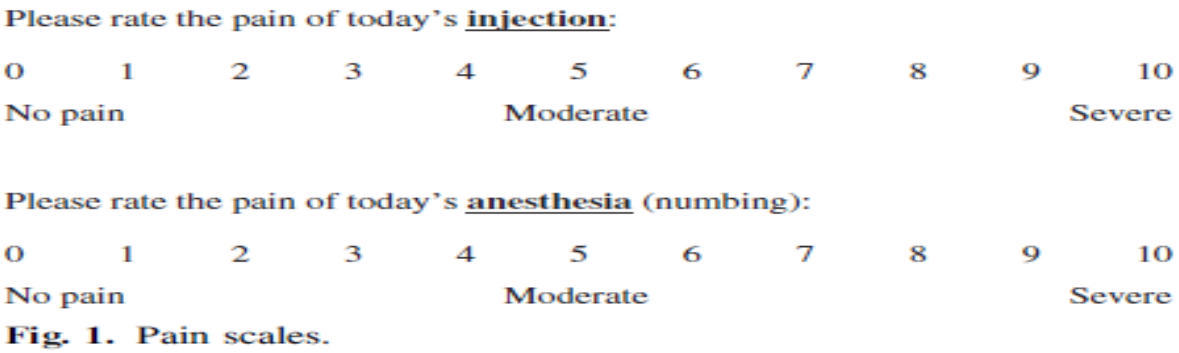



**Fig. 1.** Pain scales.

Per the summary, the pain scale scores were treated as continuous parametric variables for statistical analysis. Two-factor analysis of variance was used to look for statistical significance between the groups using blocks and treatments as the two groups. The results show that there was no statistically significant difference (P=0.28) between the pain scores from intravitreal injection. The average pain of the intravitreal injection was 3.0 with 4% lidocaine pledget (range, 0-9), 2.8 with topical proparacaine (range, 0-8), 2.3 with 2% lidocaine subconjunctival injection (range, 0-6), and 3.1 with topical tetracaine (range, 0-10). Similarly, the study showed that there was no statistically significant difference (P=0.17) between the pain scores for anesthesia (Figure 19). The average pain score from the anesthesia itself was 1.4 for 4% lidocaine pledget (range, 0-8), 0.7 for topical proparacaine (range, 0-4), 1.6 for 2% lidocaine subconjunctival injection (range, 0-6), and 1.0 for topical tetracaine (range, 0-4).

As additional analysis, the combined pain score was also calculated by adding the pain score for anesthesia and the intravitreal injection. The authors state that, this type of analysis has also been used in other studies with the goal of trying to assess the total discomfort for the procedure. The study shows that, the combined score was 4.4 for 4% lidocaine pledget, 3.5 for topical proparacaine, 3.8 for 2% lidocaine subconjunctival injection, and 4.1 for topical tetracaine. The study reported that the differences were not statistically significant (P=0.65; Figure 20).

With respect to safety, fifty-four percent of eyes receiving subconjunctival lidocaine developed a subconjunctival hemorrhage from the anesthesia. None of the other anesthetic methods caused subconjunctival hemorrhage or other None of the other anesthetic methods caused subconjunctival hemorrhage or other complications. Based on these results, the authors concluded that topical anesthesia is an effective method for limiting pain associated with intravitreal injections.

**Figure 18 : Mean injection pain scores (Blaha 2011)**

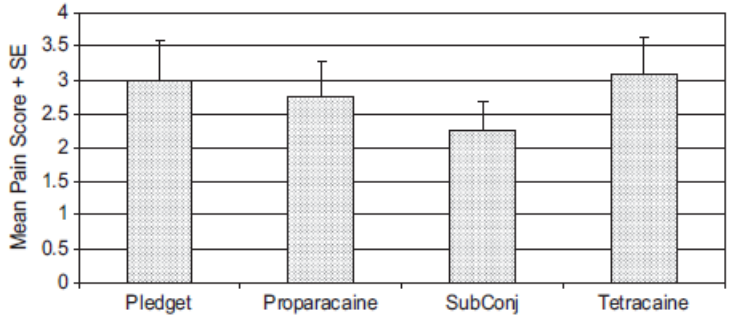



**Figure 19 : Mean anesthesia pain scores (Blaha 2011)**

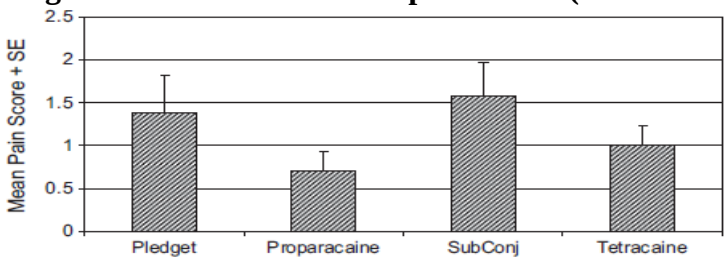
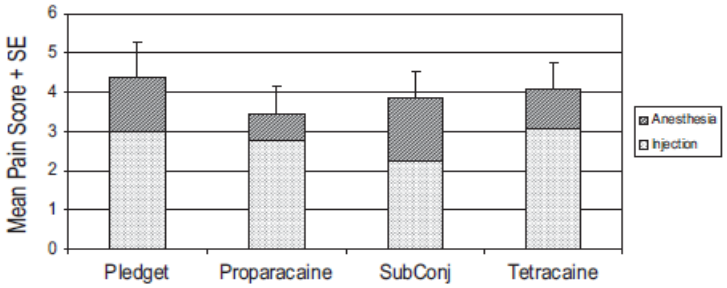



**Figure 20 : Mean combined pain scores (Blaha 2011)**




## 5.2 Supportive Efficacy Studies

In addition to the 15 key efficacy studies, the applicant submitted additional 14 studies as supportive evidence. The sections below provide brief summaries of each of the publications the applicant submitted as supportive efficacy evidence. Here also unless stated otherwise all summaries are gleaned from the publications.

### 5.2.1 Watson (1991): Topical amethocaine in strabismus surgery

This study was conducted to assess the effect of topical 1% amethocaine on post-operative analgesia requirements after strabismus surgery. In this study, a total of 40 children between the ages of 1-12 (mean of 4 years) who presented for elective surgery for correction strabismus were randomized in a 1:1 ratio to receive either 2 drops of 1% amethocaine or a saline.

The patient's pain was assessed by a blinded assessor on arrival and after 15, 30 minutes and at 1, 2, 4, 6 and 8 hours post-operation using a 4-point scale score (1=sleeping, 2=awake and quite, 3=agitated and 4=crying). For each subject the total score which is the sum of the scores across the 8 time points was calculated. Additionally, the need for additional analgesia, the pulse and respiratory rate were noted and the times of administration of any analgesics recorded. Statistical analysis was undertaken using the Chi-squared test for analgesic requirements and the Kruskal-Wallis one-way nonparametric test for assessment scores.

The study reported that there was a statistically significant difference in the mean total score in favor of the amethocaine group (11.4 (range 8-19) versus 19.5 (range 8-32); P<0.001; Kruskall Wallis). Using the total pain scores presented in Figure 21, the reviewer computed mean total scores were 11.8 and 19.5 in amethocaine group and saline group respectively (Diff: 7.3: 95% CI (3.4, 11.2)). The authors reported P-value is based on a non-parametric test.

The proportion of subjects who required no further analgesia was significantly higher in the amethocaine group compared to the control group (12(75%) vs 3 (1.5)). Only 3 (7.5%) of the 40 patients in the trial had any nausea or vomiting. One was in the control group and two were in the trial group. The authors concluded that topical 1% amethocaine provided significantly better postoperative analgesia as measured by the assessment of pain score and postoperative analgesia requirements.

**Figure 21 : Summary of total postoperative assessment scores (Watson 1991)**

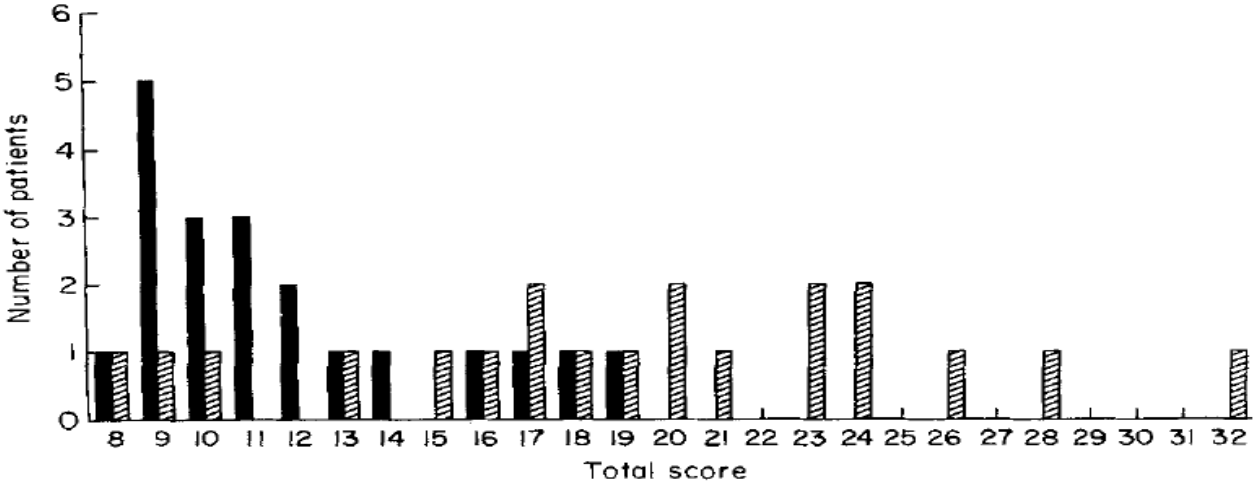



**Fig. 1.** Total postoperative assessment scores; ■, trial group; ▨, control group.

### 5.2.2 Yu et al (2003): Comparison of lidocaine 2% Gel versus amethocaine as the sole anesthetic agent for strabismus Surgery

This study was designed to compare the effectiveness of lidocaine 2% with amethocain in terms of pain control in one-stage strabismus surgery. The study enrolled a total of 14 patients (10

females and 4 males) between the ages of 21-64 (mean age of 39.3). These patients were scheduled to undergo bilateral strabismus surgery at the Hong Kong eye hospital. The patients had selected topical anesthesia as their choice of anesthetic and had successfully completed a preoperative forced duction test. The right eye of the first 7 subjects was randomized to amethocaine 1% drops and the left eye to lidocaine 2% gel. For the reaming 7 subjects, the left eye was randomized to amethocaine 1% drops and the right eye received lidocaine 2% gel. The sample size calculation assumed a standard deviation of 1.7 and an expected effect difference of 1.2.

The principal outcome measures were pain and discomfort experienced during surgery, perceived by both the patient and surgeon independently. These parameters were measured by asking the subject to mark a plain 10-cm line labeled “no pain or discomfort” on one side and “severe pain and discomfort” on the other. A score was obtained by measuring from the left side of the line to the mark in centimeters. Hence, a lower score was equated with less pain and discomfort. In addition to the pain outcome, the proportion of subjects who required additional anesthetic drops during surgery and the mean number of additional drops was reported.

The mean pain score as reported by patients was 2.6 for the eyes randomized to lidocaine gel, compared with 5.3 for the amethocaine group (Student’s t-test P =0.01; Figure 1). The mean discomfort score was 3.2 for the lidocaine group and 6.2 for the amethocaine group (P =0.01). From the surgeon’s point of view, the subjective pain score was 2.2 for eyes receiving lidocaine and 4.6 for eyes receiving amethocaine (Student’s t-test; P =0.01; Figure 2); comfort throughout surgery was 1.9 for the lidocaine group and 4.2 for the amethocaine group (P =0.01; Figure 3). Because no standard error estimates were provided and that there was no raw data, the reviewer was not able to construct confidence intervals for the mean differences or verify the reported results. Additionally, the authors reported P-vales from a Students t-test. It is not clear however if this refers to the paired t-test which should be the preferred method given the paired nature of the study design.

The proportion of subjects who required no additional anesthetic drops during surgery was 11 (78.6%) in the lidocaine group compared with 5 (35.7%) in the amethocaine group resulting in a treatment difference of 42.9% (95% CI: 6.3%, 66.7%). Note that, because of limited information, the confidence interval for the difference in proportion was constructed assuming the results from the two eyes are independent which might not be the case. The mean number of additional drops required was 0.3 (range, 0-2) for the lidocaine group and 1.6 (range, 0-6) for the amethocaine group (P=0.02; Fig 3). The authors concluded that lidocaine gel is superior to topical amethocaine (referred in this study as the standard of care) in terms of pain control.

**Figure 22: Summary of patient's subjective pain and discomfort and score (Yu 2003)**

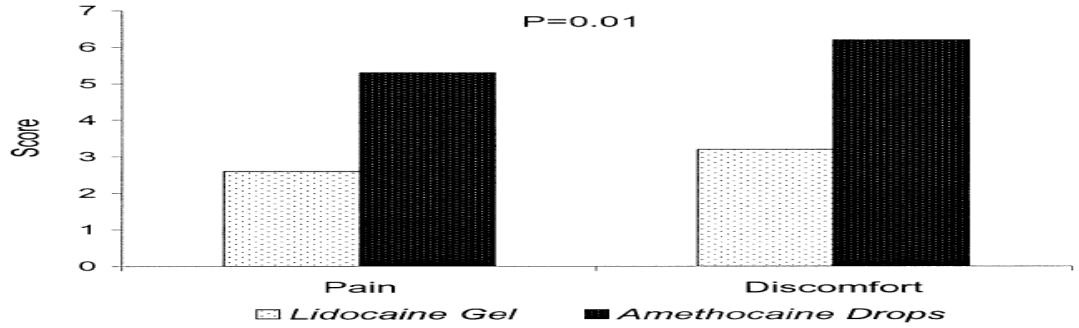



**Figure 23: Summary of surgeon subjective pain and discomfort and score (Yu 2003)**

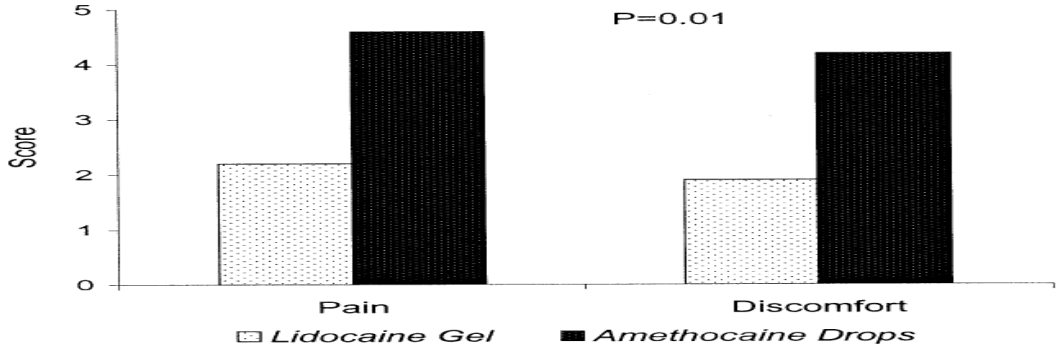
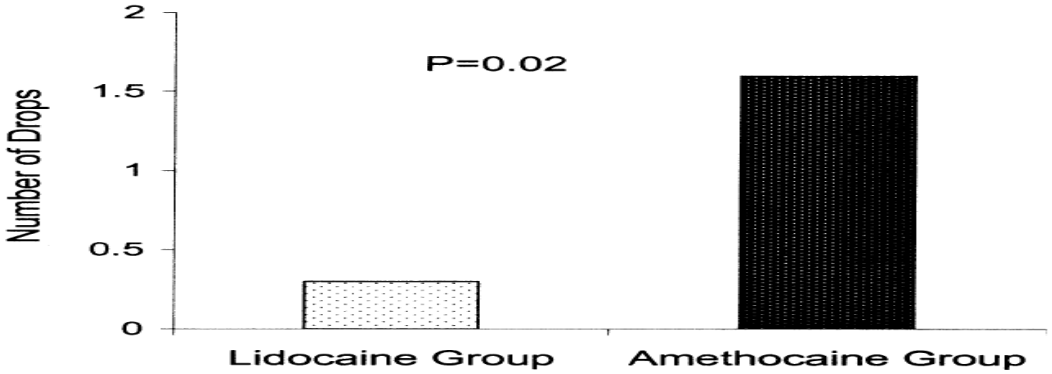



**Figure 24: Summary of mean number of additional anesthetic drops (Yu 2003)**




### 5.2.3 Anninger et al (2007): The effect of topical tetracaine eye drops on emergence behavior and pain relief after strabismus surgery

In this study, 88 subjects aged 1 to 12 years scheduled for strabismus surgery were enrolled in a double-masked randomized control trial. This study was designed to test the hypothesis that topical 1% tetracaine ophthalmic drops can decrease the intensity and incidence of postoperative pain and emergence agitation. The 88 patients were randomized to one of three

groups in a roughly 1:1:1 ratio: 28 subjects in Group A (normal saline drops before and after surgery); 29 subjects in Group B (normal saline drops before and tetracaine 1% drops after surgery); 30 subjects in Group C (tetracaine 1% drops before and after surgery).

An observer masked to group assignment assessed each patient at 5, 10, 15, 30 and 45 minutes after arriving in the post-anesthesia care unit (PACU) using both an emergence behavior scale (EBS) and a modified behavioral pain scale (MBPS).

The MBPS contains 3 indicators (Cry, facial expression and movements). Cry is scored using a 0, 1, 2, 3 or 4 scale (0=laughing or giggling, 1=not crying, 2=moaning, quite vocalization or gentle whimpering, 3=full-lunged cry or sobbing and 4=full lunged cry, clearly more than baseline full-lunged cry). Facial and movements are scored using a 0, 1, 2 or 3. For facial (0=definite positive expression, 1=neutral expression, 2=slightly negative expression and 3=Definite negative expression). For movements (0=usual movements and activity, 1=resting and relaxed, 2=partial movement or attempt to avoid pain, 3=Agitation with complex movements). For each patient, based on the MBPS, at a given measurement time, the minimum pain score of 0 represented no pain and the maximum pain score of 10 represented high pain. For statistical analysis purposes, a MBPS score of 5 or greater was considered a child in pain. The study noted that the MBPS is a validated pain scale for infants, and that its accuracy in analyzing pain in older children has not been verified. The EBS is a 4-level scale (1=asleep or awake/calm, 2=slight agitation or fussy, 3=crying and 4=trashing and crying).

Note that, in this study, rescue medication (morphine, 0.05 mg/kg) was administered to any child who was crying at two consecutive 5-minute assessments, or whose MBPS $\geq$7, or who complained of eye pain. The primary endpoint of the study was the need for rescue using morphine. The study reported that there was no significant difference between groups in PACU morphine use. No summary data is provided regarding the number of subjects who received rescue therapy. There were no statistically significant differences in patient characteristics among the three arms.

The three treatment arms were also compared with respect to the percentage of children with MBPS score of less than 5, and the percentage of patients with an EBS score of 1 or 2 using the Kruskall-Wallis test at all measurement times. Additionally, pairwise comparisons with respect to the two endpoints were performed using the Mann-Whitney U-test.

Using the MBPS, the proportion of subjects with a post-operative pain score of less than 5 was statistically significantly lower in Group A (Placebo) when compared with Groups B or C at 5 minutes after arrival to the PACU. The differences however were not statistically significant at other measurement times (15, 30 and 45 minutes) (Table 18). Using the emergence behavior scale, a significantly lower proportion of patients in Group A, as compared with Groups B and C had behavioral scores of 1 or 2 (i.e. they were crying, or crying and thrashing more), at 5, 15,

and 30 minutes after arrival to the PACU (5 minutes, p < 0.019; 15 minutes, p<0.041; 30 minutes, p <0.021; Table 19).

The authors stated that they expected significantly more patients in Group A would require rescue morphine when compared with Groups B and C, but this did not turn out to be the case. They stated that this suggests either that the tetracaine drops did not truly provide the pain relief described above or that the criteria for the administration of morphine were not sensitive enough to cause a difference in total medication given. A further consideration when applying the findings of this study to clinical practice is the fact that 1% tetracaine solution was used.

**Table 18: Summary of proportion of subjects with post-operative pain score <5 (MBPS) (Anninger 2007)**

| | A | B | C | *p** |
|---|---|---|---|---|
| Arrival | 68% | 70% | 81% | 0.53 |
| 5 min | 43% | 76%† | 77%† | 0.02 |
| 10 min | 57% | 71% | 81% | 0.36 |
| 15 min | 61% | 79% | 77% | 0.26 |
| 30 min | 63% | 71% | 84% | 0.27 |
| 45 min | 81% | 69% | 81% | 0.69 |

**p*-values are for comparison of behavior scores between all groups using the Kruskal-Wallis test.

**Table 19: Summary of proportion of subjects with postoperative emergence behavioral score of 1 or 2 (Anninger 2007)**

| | A | B | C | *P** |
|---|---|---|---|---|
| Arrival | 75% | 82% | 81% | 0.81 |
| 5 min | 50% | 79%† | 74%† | 0.02 |
| 10 min | 64% | 76% | 84% | 0.20 |
| 15 min | 60% | 90% | 94%† | 0.04 |
| 30 min | 74% | 79% | 90%† | 0.02 |
| 45 min | 90% | 81% | 95% | 0.23 |

**p*-values are for comparison of Behavior scores between all groups using the Kruskal-Wallis test.
†Indicates a $p < 0.05$ for paired comparisons to Placebo using the Mann-Whitney U-test.

**Figure 25 : Summary of maximum MBPS score (Anniniger 2007)**

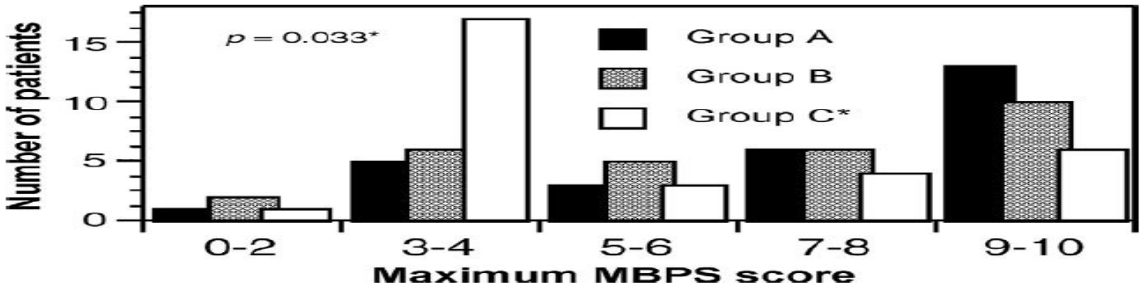



**FIG 1.** Maximum MBPS score by group. The number of patients who reached a given modified behavioral pain scale (MBPS) score in each group.

### 5.2.4 Carino et al. (1998): Topical tetracaine versus topical tetracaine plus intracameral lidocaine for cataract surgery

This study was a randomized, controlled study comparing 2 methods of anesthesia in 59 subjects (60 eyes) (24 male, 36 females aged 34 to 82 years) undergoing phacoemulsification and IOL implantation. Subjects were randomized to receive either topical tetracaine 0.5% plus intracameral BSS (n=30) or topical tetracaine 0.5% plus intracameral lidocaine 1% (n=30). There does not appear to be noticeable difference in age and gender distribution between the two arms (Table 20).

Subjects were evaluated for pain on a 4-point pain scale during surgery (0=no pain and 3-sever pain). Patient and surgeon satisfaction with anesthesia was measured on a 5-point satisfaction scale (1=extremely dissatisfied and 5=extremely satisfied). The results show that, five of the 30 eyes (17%) in the intracameral BSS group experienced more than mild intraoperative pain, which the authors defined as an anesthetic failure, requiring the addition of intravenous anesthesia. There were no anesthetic failures in the intracameral lidocaine group (Table 21). The authors reported that this difference approached statistical significance (P=0.052). The study also reported that all patients reported no pain preoperatively (i.e., after prepping and draping; Figure 26).

There was no statistically significant difference in the mean pain score after capsulorhexis in the intracameral BSS group and the intracameral lidocaine group (0.13 ± 0.35 [SD] and 0.10 ± 0.31, respectively; P = .69). Mean pain score after phacoemulsification was significantly higher in the intracameral BSS group than in the intracameral lidocaine group (0.63 ± 0.7 and 0.23 ± 0.4, respectively; P=0.019). Mean pain score at the end of the procedure was also significantly higher in the intracameral BSS group than in the intracameral lidocaine group (0.60 ± 0.6 and 0.21 ± 0.4, respectively; P=0.014).

The mean surgeon satisfaction score was significantly lower for the intracameral BSS group than for the intracameral lidocaine group (3.90 ± 1.2 and 4.73 ± 0.8, respectively; P=.0007). There was no significant difference in the mean patient satisfaction score (4.60 ± 0.6 and 4.70 ± 0.8, respectively; P=0.18) and in patient preference for the type of anesthesia for the other eye (80% and 90%, respectively).

The authors concluded that this study demonstrated a statistically significant lower patient subjective pain score in the intracameral lidocaine group than in the intracameral BSS group at 2 points: the completion of phacoemulsification and the completion of the procedure. There was no significant between-group difference in the subjective pain scores preoperatively and at the completion of the capsulorhexis. They also concluded that there was no statistically significant between-group difference in patient satisfaction despite higher subjective pain scores in the BSS group.

**Table 20: Patient demographics (Carino 1998)**

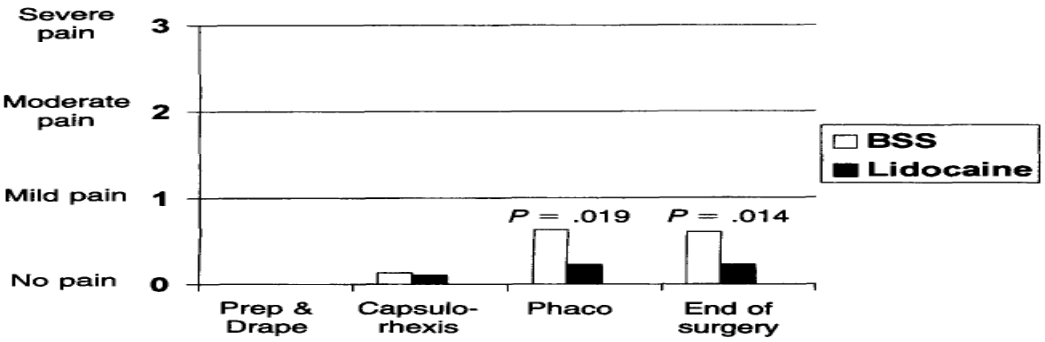
| Characteristics | Treatment | |
|---|---|---|
| | Tetracaine + BSS N=30 | Lidocaine N=30 |
| Age (years)* | 69.9 (40 -82) | 67.1 (34 to 81) |
| Sex: Male/female | 10/20 | 16/14 |

*Data are presented as mean (range)

**Table 21: Distribution of pain scores at the predetermined intervals (Carino 1998)**

| Predetermined Interval | Pain Score, Number of Patients (%) | | | |
|---|---|---|---|---|
| | No Pain (0) | Mild Pain (1) | Moderate Pain (2) | Severe Pain (3) |
| After prep/drape | | | | |
| Intracameral BSS | 30 | 0 | 0 | 0 |
| Intracameral lidocaine | 30 | 0 | 0 | 0 |
| Capsulorhexis | | | | |
| Intracameral BSS | 26 (86.7) | 4 (13.3) | 0 | 0 |
| Intracameral lidocaine | 27 (90.0) | 3 (10.0) | 0 | 0 |
| Phacoemulsification | | | | |
| Intracameral BSS | 15 (50.0) | 11 (36.7) | 4 (13.3) | 0 |
| Intracameral lidocaine | 23 (76.7) | 7 (23.3) | 0 | 0 |
| End of surgery | | | | |
| Intracameral BSS | 14 (46.7) | 14 (46.7) | 2 (6.7) | 0 |
| Intracameral lidocaine | 23 (76.7) | 7 (23.3) | 0 | 0 |

**Figure 26 : Summary of interoperative pain reported score (Carino 1998)**




### 5.2.5 Fazel et al. (2008) Retrobulbar versus Topical Anesthesia for Phacoemulsification

This was a randomized, controlled study comparing retrobulbar versus topical anesthesia in 564 subjects (256 male, 308 female) undergoing phacoemulsification. Subjects were randomized to receive either tetracaine 0.5% eye drops 5 times within 25 minutes before surgery plus intracameral lidocaine 2% (n=282) during surgery **or** 4ml of lidocaine 2% in the retrobulbar space (n=282). All subjects received 2 mcg/kg fentanyl 5 minutes before the start of the procedure.

Pain was assessed by the subjects immediately after surgery using a 10-point pain scale (0=no pain and 10=extreme pain). In the retrobulbar group, 235 (83%) subjects and 238 (84%) subjects in the topical group reported minimal discomfort (maximum score of 2) or no pain (score of 0). Mean pain score was 1.13 ± 1.36 in the topical group compared to 1.14 ± 1.47 in the retrobulbar group. The difference in mean pain score was not significant (P=0.92; Table 22). The study also reported that there was no statistically significant difference in the number of patients that needed additional sedation (17 patients in the retrobulbar group and 14 subjects in the topical group; P=0.45).

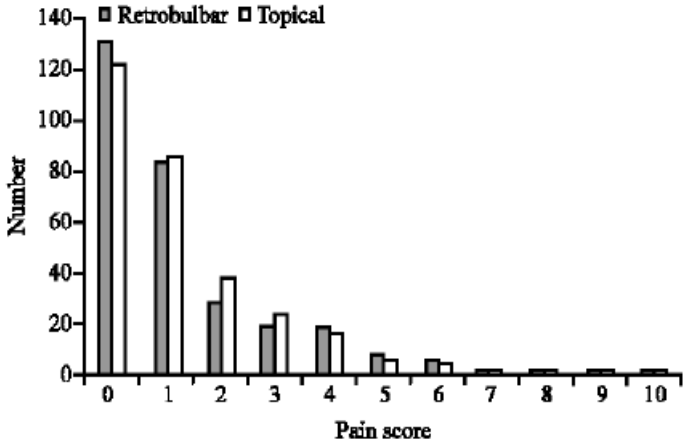
Based on these results, the authors concluded that, the study demonstrated that both topical anesthesia with tetracaine 0.5% with intracameral lidocaine 2% and retrobulbar lidocaine 2% were effective in providing pain relief in subjects undergoing phacoemulsification procedures.

**Table 22: Comparative results in the two study groups (Fazel 2008)**

| Variables | Treatments | | P-value |
|---|---|---|---|
| | Retrobulbar N=282 | Topical N=282 | |
| Age (Years) | 71.5±8.98 | 70.54±8.35 | 0.28 |
| Sex (M/F) | 129/153 | 127/155 | 0.46 |
| Preoperative visual acuity | 0.27±0.16 | 0.4±0.62 | 0.14 |
| Bulbus length (mm) | 23.17±1.48 | 23.34±1.2 | 0.13 |
| Preoperative IOP (mm Hg) | 15.96±2.58 | 15.74±2.71 | 0.41 |
| Postoperative visual acuity | 0.43±0.21 | 0.52±0.64 | 0.94 |
| Patient visual pain score (0-10) | 1.14 ± 1.47 | 1.13 ± 1.36 | 0.92 |

Data is presented as Mean±SD.

**Figure 27 : Summary of patient reported pain scores after surgery (Fazel 2008)**



### 5.2.6 Habib et al. (1993) Subconjunctival Bupivacaine versus Topical Amethocaine in Strabismus surgery

This study was a randomized, observer-masked, controlled study of pain relief following topical anesthesia in 40 children (18 male, 22 female) aged 4.7 years (range 2-8 years) undergoing strabismus surgery. Subjects were randomized to receive a subconjunctival injection of 0.25 ml of bupivacaine 0.5% (n=20) at the end of surgery or 2 drops of tetracaine (amethocaine) 1% eye drops (n=20) prior to and at the end of surgery.

Subjects were assessed for pain by the subject's nurse at 30 minutes, 1, 2 and 4 hours after surgery using a 4-point scale from 1 sleeping to 4 crying. The scores at the 4 time points for each subject were summed to produce a total pain score. The mean total pain scores for the bupivacaine group was 7.35 (range 5-10) and 8.15 (range 6-11) for the tetracaine group. The difference was not statistically significant (P=0.13).

Per the study report, although subconjunctival bupivacaine consistently achieved better analgesia than amethocaine at the 30 minute, 1, 2 and 4 hour intervals after surgery, this did not reach statistical significance (Figure 28). The authors state that, at the beginning of the study, it was proposed in the protocol that a mean difference of 2.0 was required to label one method more effective than the other. The observed difference in the total scores of the two groups was significantly less than the expected difference of 2.0 (t=-2.35, P=0.01). There was no significant difference between the two groups in patients requiring oral paracetamol suspension for analgesia. No patient in either group required pethidine.

Based on these results, the authors concluded that, the study showed that subconjunctival injection of bupivacaine 0.5% and topical tetracaine 1% were equally effective in reducing post-operative pain in children undergoing strabismus surgery.

**Figure 28 : Summary of Total Pain Score and Pain score at different times (Habib 1993)**

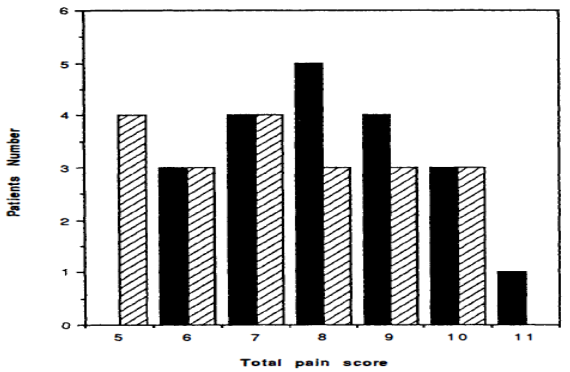



**Fig. 1.** *Total post-operative pain assessment scores. Black columns, amethocaine; hatched columns, bupivacaine.*

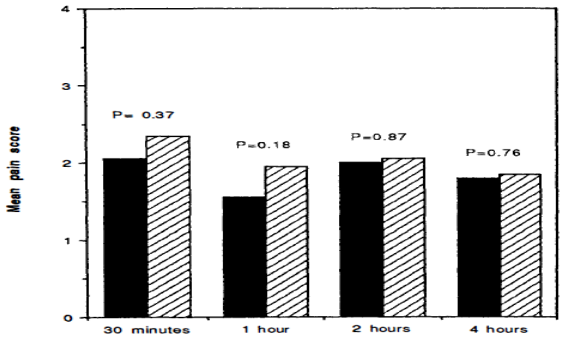



**Fig. 2.** *Mean pain scores in the two groups as measured at different time intervals. Black columns, bupivacaine; hatched columns, amethocaine.*

### 5.2.7 Hamilton el al (1998): Topical anesthesia: Proxymetacaine versus Amethocaine for corneal phacoemulsification

This study was a randomized, controlled study. The study enrolled 40 subjects having routine clear corneal phacoemulsification. Subjects were randomized in a 1:1 ratio to receive a single drop without preservative of tetracaine (amethocaine) 1% (n=20) or proxymetacaine 0.5% eye drops (n=20). The anesthetic drops were administered into occasions 1 minute apart just before surgery. Both groups were supplemented during surgery with intracameral lignocaine 1%.

Per the study summary, within 2 hours of surgery, the level of patient discomfort was assessed using a 10-point pain scale where 0=no pain or discomfort and 10= excruciating pain. The level of discomfort was assessed for at three time points: preoperatively (i.e., on instillation of the topical anesthetic agent); intraoperatively (i.e., during surgery); postoperatively (i.e., during the first hour after surgery).

A Student t test was used to assess the significance of the differences between the 2 groups. The results show that, no patient needed additional analgesia throughout the procedure or required intravenous sedation preoperatively or intraoperatively. There was a statistically significant difference in the mean preoperative pain score (P<0.01). The mean pain score in the Proxymetacaine group was 0.25 compared to 2.70 in the Amethocaine group. The study also showed that, the mean intraoperative and postoperative pain scores in the 2 groups were similar. The difference between groups was not significant (Table 23).

Based on these results, the authors concluded that, both tetracaine and proxymetacaine produce adequate and similar levels of topical anesthesia during and after clear corneal cataract surgery but proxymetacaine causes less pain on instillation than tetracaine.

**Table 23: Summary of patient pain scores (Hamilton 1998)**

| Stage | Group | | |
|---|---|---|---|
| | Proxymetacaine N=20 | Amethocaine N=20 | P-value |
| Preoperative | 0.25 (0.64) | 2.70 (3.94) | <0.01 |
| Intraoperative | 0.25 (0.49) | 0.25 (0.72) | NS |
| Postoperative | 0.05 (0.22) | 0.15 (0.49) | NS |

Data is presented as Mean (SD); NS: not significant.

### 5.2.8 Irle et al (2003):

This study evaluated sensitivity to pain during cataract surgery in 111 subjects following topical anesthesia. Subjects received tetracaine 1% eye drops (n=62) applied 3 times or lidocaine 2% gel (n=49) applied once postoperatively. Subjects assessed pain intensity after surgery using a 10-point pain scale. Mean pain sensitivity in subjects treated with tetracaine (1.77) was reported to be significantly less (p<0.043) then in subjects treated with lidocaine (2.22).

In conclusion, both tetracaine 1% eye drops and lidocaine 2% gel are suitable topical anesthetics for cataract surgery with tetracaine being better for pain elimination.

*Reviewer's remark: This study is summarized in a foreign language. The above summary is based on an English abstract included in the publication.*

### 5.2.9 Perez-Castanedo et al. (1998):

This study was a randomized, controlled study comparing the efficacy of topical anesthesia and retrobulbar anesthesia in 260 subjects (88 male, 172 female) undergoing cataract surgery. Subjects were randomized to receive either tetracaine 0.5% eye drops plus intravenous fentanyl and propofol with continuous sedation (n=129) or lidocaine 2% in the retrobulbar space and hypnotic doses of intravenous propofol (n=131).

An ophthalmologist evaluated anesthesia by examination of whether the eye remained fixed in the center, if blepharospasm appeared or if the anterior chamber of the eye collapsed. Subjects reported the intensity of discomfort on a 6-point scale.

The lidocaine treated group reported significantly fewer instances of ineffective anesthesia (8 vs 22) and fewer negative evaluations by the ophthalmologist (7 vs 18). More subjects in the tetracaine group reported discomfort (46 vs 9) although most of the complaints were of slight discomfort.

*Reviewer's remark: This study is summarized in a foreign language. The above summary is based on an English abstract included in the publication.*

### 5.2.10 Ting et al. (2009): Management of Ocular Trauma in Emergency (MOTE) Trial: A pilot randomized double-blinded trial comparing topical amethocaine with saline in the outpatient management of corneal trauma

This study was a randomized, double-masked placebo-controlled study. The study enrolled 47 male subjects with minor (uncomplicated) corneal injury. Subjects were randomized to tetracaine (amethocaine) 0.4% eye drops or placebo (saline) once hourly as needed for pain relief supplemented by oral analgesia as required. The objective of the study was to assess whether topical 0.4% amethocaine self-administered to a maximum recommended frequency of once every hour for 36–48 h is safe in the management of uncomplicated corneal injury in patients discharged from the ED.

Baseline characteristics, including corneal injury type, were similar in both groups (Table 24). Pain was assessed in the emergency department and 36-48 hours after recruitment using a patient diary with a visual analog pain scale. The study reported that the mean cumulative pain

score was lower for the tetracaine group and the need for oral analgesia for eye pain did not differ between treatment groups.

The authors then concluded that, compared with saline drops, amethocaine eye drops are not definitely safe but they are effective for topical analgesia in minor corneal injury. They also stated that, until further definitive studies, topical nonsteroidal agents or long-lasting artificial tears may be preferred for the topical analgesia of minor corneal injury.

**Table 24: Patient demographics (Ting 2003)**

| Characteristics | Treatment | |
|---|---|---|
| | **Tetracaine N=22** | **Saline N=25** |
| Mean Age (Years) | 35.1 | 33.6 |
| Mean time from Injury | 13.8 | 15.8 |
| Injury type: n (%) | | |
| Corneal abrasion | 8 (36) | 7 (28) |
| Corneal foreign body | 9 (41) | 11 (44) |
| Welding flash burn | 4 (18) | 6 (24) |
| Welding flash burn and Corneal foreign body | 1 (5) | 1 4) |

### 5.2.11 Verma el al. (1995): A prospective, double-masked trial to evaluate the role of topical anesthetics in controlling pain after photorefractive keratectomy

This study was a randomized, controlled study. The purpose of this study was to investigate the role of 1% tetracaine in controlling pain after photorefractive keratectomy. The study enrolled 44 subjects (15 male, 29 female aged 25-72 years) with pain after photorefractive keratectomy (PRK). Eligible subjects are over the age of 24 who have a refraction of -3 to -6 diopters. They are also expected to have an astigmatism of less than -1.5 and have a visual acuity of more than 20/30.

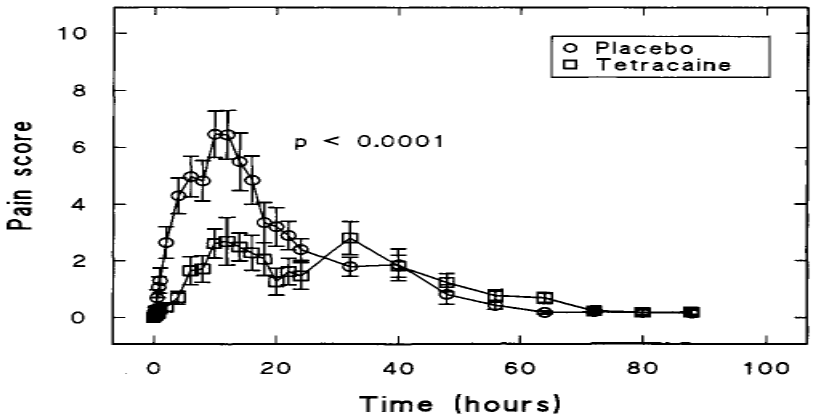
The authors state that, a sample size of 44 was deemed appropriate to give statistically significant results. Subjects were randomized in a 1:1 ratio to receive tetracaine hydrochloride 1% eye drops or placebo (saline) eye drops instilled at 30 minute intervals during waking hours for 24 hours after surgery. Subjects also received 2 coproxamol (paracetamol + dextropropoxyphene) tablets every 8 hours for 2 days. Pain was measured on a 10 cm visual analog pain scale (with "no pain" written at one end and "worst pain imaginable" at the other) for 4 days after surgery (at 15 minute intervals initially for 1 hour and then every 2 hours for 24 hours then every 8 hours for 3 days).

The study reported that, the pain levels in both the placebo and tetracaine cohorts rose rapidly to a maximum over the first 10 hours after surgery and then declined to zero by 72 hours (Figure 29). The authors also stated that the maximum pain level was 6.5 for the placebo group and 2.5 for the tetracaine group. Although individual pain thresholds vary tremendously on average, a value of 3 was deemed as acceptable discomfort. No significant difference was observed in pain

levels experienced by the two refractive groups. Per the authors, subjects in the tetracaine group rated the postoperative period as not painful in 85% of cases compared to 39% in the placebo group.

Based on these findings, the authors concluded that, this study demonstrated that tetracaine provides pain control after PRK surgery without significant effects on the efficacy of the refractive procedure.

**Figure 29 : Graphical presentation of pain for all patients: Mean +SD (Verma 1995)**




### 5.2.12 Verma (1997): A comparative study of the duration and efficacy of tetracaine 1% and bupivacaine 0.75% in controlling pain following photorefractive keratectomy (PRK)

This study was a randomized, controlled study to evaluate pain control with 2 different topical anesthetics following PRK. In this study, 38 subjects (10 male, 29 female). between the age of 26 to 73 year were in enrolled. Subjects were randomized in a 1:1 ratio to receive either tetracaine 1% eye drops or bupivacaine 0.75% eye drops every 30 minutes for 24 hours after surgery.

Per the authors, pain was recorded over a 4 day period using a visual analog pain scale every 15 minutes for an hour when awake, at 2 hourly intervals for 24 hours and then at 8 hour intervals for 3 days. In addition, per the authors, to obtain a detailed understanding of the control of pain intensity over the duration of a single instillation, a further sub-study was undertaken just prior to the period of maximum pain. In this sub-study, patients were asked to complete a separate set of pain charts at 5 minute intervals between 5 hours and 5 hours and 30 minutes after surgery. The recordings at 5 hours and 5 hours and 30 minutes would represent the pain levels immediately after instillation of two successive drops. By contrast, the 5 hour 25 minute reading would relate to the level of pain just prior to drop instillation.

The results show that the pain profile for both tetracaine and bupivacaine are similar in that pain levels rise rapidly to a maximum over the first 12 hours after surgery and then decline to zero by 96 hours (Figure 30). Per the authors, on the pain scale 2.0 represented discomfort and 3.5 pain. The maximum pain score for the tetracaine group was 3.5 and that for bupivacaine was 5.5.

The study states that, the area under the pain curve was calculated for each patient in the study and the total area calculated for each group. The difference in area between the two groups just reached statistically significant levels (P=0.05). The authors also state that, although more pronounced in the tetracaine group, both cohorts showed a transient increase in pain levels at 30 hours representing a heightened appreciation of pain after cessation of anaesthetic drops at 24 hours. The duration of action of the drops is represented in
Figure 31. The shape of the curve is similar for both anaesthetics, but pain suppression by tetracaine was significantly greater. Pain levels were the lowest 5 minutes after instillation of the drops and gradually reached a maximum by 30 minutes. Time “0” represented the pain levels immediately after drop instillation and time "30" immediately pre-instillation. Both groups reported that the drops were most effective in the first 20 minutes post-administration. Based on these results, the authors concluded that, their study has shown that tetracaine is more effective than bupivacaine in controlling pain following PRK.

**Figure 30 : Graphical presentation of pain profile (Verma 1997)**

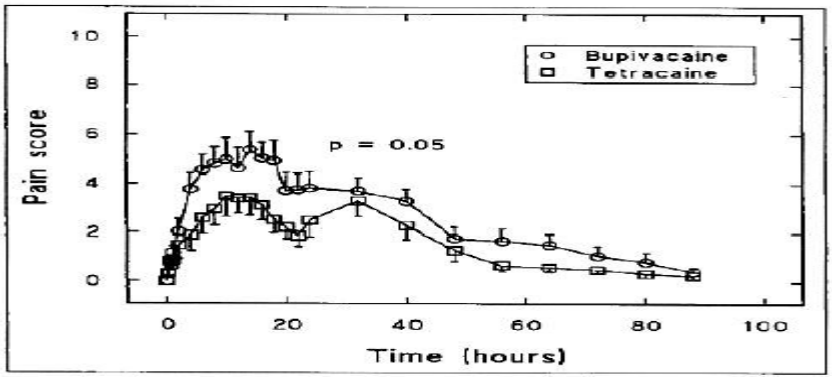
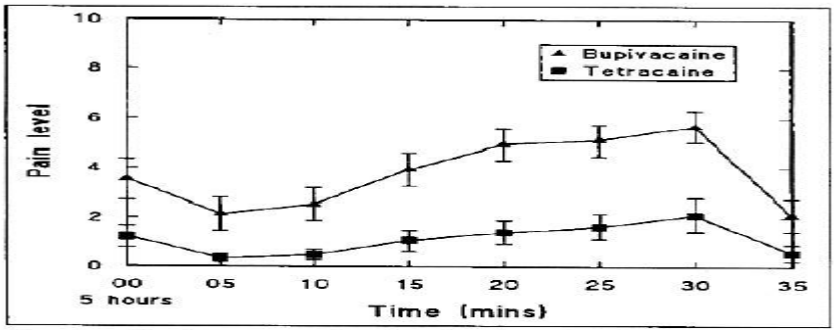



**Figure 31 : Graphical presentation of duration of action (Verma 1997)**



### 5.2.13 Waldman (2014): Topical Tetracaine Used for 24 Hours Is Safe and Rated Highly Effective by Patients for the Treatment of Pain Caused by Corneal Abrasions: A Double-blind, Randomized Clinical Trial

This study was a randomized, double-masked, placebo-controlled study of tetracaine vs saline (Placebo). The study enrolled a total of 116 subjects into (104 male, 12 female aged 17 to 74 years) with uncomplicated corneal abrasions or corneal foreign bodies. Subjects were randomized to receive either tetracaine HCl 1% eye drops (n=59) or saline eye drops (n=57) applied up to every 30 minutes while awake for 24 hours.

The primary objective of the study was to evaluate the effects of the treatments on corneal healing. The study evaluation of pain using a 100-mm visual analog pain scale as a secondary endpoint. Pain was recorded every 2 hours while awake for 48 hours. In addition, patient perceived overall effectiveness was recorded using a 10-point numeric rating scale obtained during telephone interviews. Analgesia was supplemented orally with acetaminophen (paracetamol) taken as two 500 mg tablets every 4 hours for the first 24 hours.

Eighty-five subjects completed pain questionnaires. Of these, 65 subjects provided pain scores on arrival (tetracaine n= 32; saline n=33) with a mean score of 54.6 mm for tetracaine and 48.0 for saline. There was no clinical difference in pain scores between the groups. The average difference in pain over the first 24 hours was 0.44 mm (p=0.259) and 0.53 mm (p=0.149) over the first 48 hours in favor of tetracaine. Subjects in the tetracaine group rated the overall effectiveness significantly higher (P<0.0005) than those treated with saline (7.7 vs 3.9 respectively).

Based on these results, the authors concluded that, in subjects with uncomplicated corneal abrasions, tetracaine demonstrated no difference to placebo (saline) with regard to pain ratings but patients perceived tetracaine to be significantly more effective than saline. The authors stated that, the lack of a significant difference could be due to the fact that in the majority of cases the pain from a corneal abrasion dissipates by about 24 hours and also due to the relatively small numbers of subjects who completed the pain questionnaire. They also stated that, the difference between the results of the pain scores and the patient perception of effectiveness could be due to the wearing off of the analgesic effect of tetracaine following the initial rapid relief and also due to the burning sensation on instillation of tetracaine.

**Table 25: Patient demographics (Waldman 2014)**

| Characteristic | Tetracaine (*n* = 59) | Saline (*n* = 57) |
|---|---|---|
| Age (yr), median (range) | 37.0 (17*–72) years | 38.0 (19–74) years |
| Sex | | |
| Male | 55 (93.2) | 49 (86.0) |
| Female | 4 (6.8) | 8 (14.0) |
| Ethnicity | | |
| European | 37 (62.7) | 32 (56.1) |
| Māori | 4 (6.8) | 4 (7.0) |
| Other | 0 | 2 (3.5) |
| Did not answer | 18 (30.5) | 19 (33.3) |
| Mechanism of injury | | |
| Metallic FB | 30 (50.8) | 30 (52.6) |
| Dirt FB | 1 (1.7) | 5 (8.8) |
| Dust FB | 7 (11.9) | 8 (14.0) |
| Wood FB | 5 (8.5) | 2 (3.5) |
| Direct trauma | 8 (13.6) | 7 (12.3) |
| Ultraviolet | 3 (5.1) | 0 |
| Unknown | 5 (8.5) | 3 (5.3) |
| Other | 0 | 2 (3.5) |
| Pain on arrival | (*n* = 32) | (*n* = 33) |
| median (range, low-high) | 54.6 mm (10–98) | 48.0 mm (0–96) |

*One 17-year-old patient enrolled with parental consent.
FB = foreign body.
Data are reported as *n* (%) unless otherwise stated.

### 5.2.14 Young (2009): Randomised controlled trial on the effectiveness of lidocaine gel vs tetracaine drops as the sole topical anaesthetic agent for primary pterygium surgery

This study was a prospective randomized, controlled trial evaluating the effectiveness of 2 topical anesthetic treatments in primary pterygium surgery. The study enrolled a total of 40 subjects (18 male, 22 female aged 26-79 years (mean age 60.80)) who were scheduled to undergo primary pterygium surgery at Prince of Wales Hospital were recruited. Per the authors, the sample size of 40 is determined assuming a standard deviation of 1.7 for the visual analogue pain scale and an expected effect difference in scoring of at least 2. Eligible subjects were randomized to receive either tetracaine hydrochloride 1% eye drops (n=21) or lidocaine hydrochloride 2% gel (n=19). Additional tetracaine drops were given to subjects experiencing pain preoperatively.

The primary outcome was the pain experienced during and after surgery. Pain and discomfort was reported by the subject and physician on a 10-point linear analog scale (0=no pain and 10=worst pain) at first incision, at pterygium body excision, during conjunctival suturing and immediately following surgery. Per the authors, statistical analysis was performed using Student's t-test, and the P-values less than 0.05 were considered statistically significant.

There were 12 female and nine male patients in the tetracaine group, and 10 female and nine male patients in the lidocaine gel group. The mean surgical duration for tetracaine hydrochloride 1% was 25.33±5.29 min, and 24.21±4.85 min for lidocaine hydrochloride 2% gel. There was no statistically significance difference in mean age, sex, size, and surgical duration between two groups (P>0.05, Student's t-test; Table 26).

There was no statistically significant difference in the patient reported mean pain scores at first incision (0.71 ± 1.10 vs 0.53 ± 1.07, p=0.59), during pterygium excision (3.98 ± 2.18 vs 3.03 ± 2.35) or immediately following surgery (1.10 ± 1.48 vs 0.42 ± 0.69, p=0.078) for the tetracaine

and lidocaine groups respectively. However, during conjunctival suturing lidocaine achieved a significantly superior difference in mean pain score compared to tetracaine (0.47 ± 0.84 vs 1.43 ± 1.66, p=0.03). The mean number of additional drops in the lidocaine group was also significantly less than in the tetracaine group (0.16 ± 0.11 vs 0.67 ± 0.09, p=0.001; Table **27**).

From the surgeon's point of view There was a statistical significant difference in the mean pain scores for all the stages. The surgeon recorded mean pain scores at stage 2 was 2.84±1.07 for eyes receiving lidocaine gel and 4.52±1.03 for eyes receiving tetracaine drops (Table 28). The study also reported that, for the tetracaine group, in 10 out of the 21 cases, no additional tetracaine was required. Eight cases required one additional drop of tetracaine and three cases required two addition drops of tetracaine. In the lidocaine group, there were 16 out of the 19 cases in which no additional tetracaine drops were added. Only three eyes required the addition of one extra drop.

Based on these results, the authors concluded that, both treatments resulted in effective anesthesia for pterygium surgery with lidocaine producing slightly lower mean pain scores than tetracaine and requiring less supplemental topical anesthesia.

**Table 26: Demographic and baseline characteristics (Young 2009)**

| | *Tetracaine 1% drop group (n = 21)* | *Lidocaine 2% gel group (n = 19)* | *P-value (Student's t-test)* | *Combined* |
|---|---|---|---|---|
| Age (years) | 62.10 ± 11.47 | 59.37 ± 12.67 | 0.48 | 60.80 ± 11.97 |
| Sex | Male = 9<br>Female = 12 | Male = 9<br>Female = 10 | | Male = 18<br>Female = 22 |
| Nasal/temporal | Nasal = 21 | Nasal = 17<br>Temporal = 2 | | Nasal = 38<br>Temporal = 2 |
| Laterality | Left = 11<br>Right = 10 | Left = 11<br>Right = 8 | | Left = 22<br>Right = 18 |
| Size (length in mm) | 3.93 ± 1.11 | 3.87 ± 1.19 | 0.87 | 3.90 ± 1.13 |
| Size (width in mm) | 5.36 ± 1.60 | 5.55 ± 0.97 | 0.68 | 5.45 ± 1.32 |

**Table 27: Patient reported mean pain score (Young 2009)**

| *Stages* | *Tetracaine 1% drop (n = 21)* | *Lidocaine 2% gel (n = 19)* | *P-value (Student's t-test)* |
|---|---|---|---|
| Stage 1 | 0.71 ± 1.10 | 0.53 ± 1.07 | 0.59 |
| Stage 2 | 3.98 ± 2.18 | 3.03 ± 2.35 | 0.19 |
| Stage 3 | 1.43 ± 1.66 | 0.47 ± 0.84 | 0.03 |
| Stage 4 | 1.10 ± 1.48 | 0.42 ± 0.69 | 0.078 |

**Table 28: Surgeon reported mean pain score (Young 2009)**

| *Stages* | *Tetracaine 1% drop (n = 21)* | *Lidocaine 2% gel (n = 19)* | *P-value (Student's t-test)* |
|---|---|---|---|
| Stage 1 | 1.76 ± 0.99 | 1.11 ± 0.94 | 0.039 |
| Stage 2 | 4.52 ± 1.03 | 2.84 ± 1.07 | 0.0005 |
| Stage 3 | 2.24 ± 0.62 | 1.11 ± 0.81 | 0.0005 |
| Stage 4 | 1.14 ± 0.48 | 0.32 ± 0.48 | 0.0005 |

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/
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ABEL T ESHETE
11/06/2018

YAN WANG
11/06/2018
Concur with the overall conclusion.

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**
**CENTER FOR DRUG EVALUATION AND RESEARCH**

# PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

| | |
|---|---|
| Application number: | 210821 |
| Supporting document/s: | N001 |
| Applicant's letter date: | 2-22-2018 |
| CDER stamp date: | 2-22-2018 |
| Product: | Tetracaine hydrochloride ophthalmic solution 0.5% |
| Indication: | For procedures requiring a rapid and short-acting topical ophthalmic anesthetic |
| Applicant: | Valeant Pharmaceuticals Ireland<br>3013 Lake Dr.<br>Dublin 24, Ireland |
| Review Division: | Division of Transplant and Ophthalmology Products |
| Reviewer: | Aaron Ruhland, PhD |
| Supervisor/Team Leader: | Lori Kotch, PhD, DABT |
| Division Director: | Renata Albrecht, MD |
| Project Manager: | Eithu Lwin |

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# 1 Executive Summary

## 1.1 Introduction

The Applicant has submitted this New Drug Application to support approval of Tetracaine Hydrochloride Ophthalmic Solution, 0.5% by topical ophthalmic instillation for procedures requiring a rapid and short-acting topical ophthalmic anesthetic. Tetracaine is an ester-linked local anesthetic that prevents the generation and the conduction of nerve impulses. The drug product has been marketed in the United States since 1992. The Applicant has submitted this application as a 505(b)(2) with limited nonclinical data to support approval. Although the Applicant indicates reliance on several listed drugs on *attachment 1 to Form 356H*, no data for these listed drugs was used/needed to support the approval of the current NDA; all nonclinical elements of the support were provided by published literature or an extended, safe history of clinical use.

## 1.2 Brief Discussion of Nonclinical Findings

All applicable nonclinical elements required to be addressed under 21 CFR314.50 (pharmacology, pharmacokinetics, systemic toxicology, ocular toxicology, effects of the drug on reproduction and on the developing fetus , carcinogenicity) were addressed in the application. The Applicant referenced published nonclinical studies which characterized tetracaine pharmacology, safety pharmacology, ocular absorption properties, effect on tear dynamics and effect on intraocular pressure. In dogs, intravenously administered tetracaine hydrochloride decreased blood pressure, heart rate, cardiac output, and stroke volume at a dose of 10 mg/kg and increased pulmonary arterial pressure at a dose of 9 mg/kg. Intravenously administered tetracaine hydrochloride at a dose of 3 mg/kg induced convulsions in dogs. Ocular effects following topical instillation described in the referenced studies include a temporary decrease in intraocular pressure and reduced tear production and turnover. No other ophthalmic toxicity was reported, and the safety of the drug product is supported by a long history of clinical use. Regarding its mutagenic, carcinogenic, reproductive and developmental toxicity potential, the Applicant states that no published articles were found in the published literature relevant for topical ocular tetracaine hydrochloride. Statements describing these lacks of published data are included in the labeling.

## 1.3 Recommendations

### 1.3.1 Approvability: Approvable from a Pharmacology/Toxicology perspective

### 1.3.3 Labeling (Sections relevant to the Pharmacology/Toxicology discipline)

| Applicant's proposed text | FDA suggested edits |
|---|---|
| **8 USE IN SPECIFIC POPULATIONS** | |

| | |
|---|---|
| **8.1 Pregnancy**<br>Risk Summary<br>There are no adequate and well-controlled studies with Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% in pregnant women. Animal developmental and reproductive toxicity studies with tetracaine hydrochloride have not been reported in the published literature. | **8 USE IN SPECIFIC POPULATIONS**<br><br>**8.1 Pregnancy**<br><br>Risk Summary<br>There are no adequate and well-controlled studies with Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% in pregnant women. Animal developmental and reproductive toxicity studies with tetracaine hydrochloride have not been **conducted**. ~~reported in the published literature~~ |
| **8.2 Lactation**<br>Risk Summary<br>There are no data to assess whether Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is excreted in human milk or to assess its effects on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% and any potential adverse effects on the breastfed child from Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% (b) (4) | **8.2 Lactation**<br>Risk Summary<br>There are no data to assess whether Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is excreted in human milk or to assess its effects on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% and any potential adverse effects on the breastfed child from Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%. (b) (4) |
| **8.3 Females and Males of Reproductive Potential**<br>No human data on the effect of Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% on fertility are available. | -no suggested edits; text is consistent with current approved labeling in PLLR format . |
| **12.1 Mechanism of Action**<br>(b) (4) the initiation and (b) (4) impulses thereby effecting local anesthesia. | -Is not consistent current approved labeling. Suggested text:<br><br>**12.1 Mechanism of Action**<br>Tetracaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses thereby affecting local anesthesia. |

| 13 NONCLINICAL TOXICOLOGY | 13 NONCLINICAL TOXICOLOGY |
|---|---|
| **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**<br>Studies to assess the genotoxicity of tetracaine hydrochloride have not been reported in the published literature. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of tetracaine hydrochloride. Animal studies to assess the effects of tetracaine hydrochloride on fertility have not been reported in the published literature | **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**<br>Studies to assess the **carcinogenic or** genotoxic~~ity~~ **potential** of tetracaine hydrochloride have not been **conducted.** ~~Long-term animal studies have not been conducted to evaluate the carcinogenic potential of tetracaine hydrochloride.~~ Animal studies to assess the effects of tetracaine hydrochloride on fertility have not been **conducted.** ~~reported in the published literature~~ |

# 2 Drug Information

## 2.1 Drug

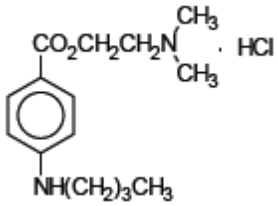
CAS Registry Number: 136-47-0

Drug Product Name: Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5%

Chemical Name: 2-(Dimethylamino)ethyl p-(butylamino)benzoate monohydrochloride

Molecular Formula/Molecular Weight: $C_{15}H_{24}N_2O_2 \cdot HCl$ / 300.82 g/mol

Structure:




Pharmacologic Class: Ester local anesthetic

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

The Applicant references:

- NDA 208135: Tetracaine Hydrochloride Ophthalmic Solution, 0.5%

- *Attachment 1 to form 356H; "The Sponsor has not conducted any additional nonclinical studies to support this NDA but instead is providing a summary of the published literature and is relying on the Agency's previous assessment of the nonclinical safety of tetracaine from the approved NDAs that contain this active pharmaceutical ingredient:*

    - *Tetracaine Hydrochloride Ophthalmic Solution 0.5% (NDA 208135)*
    - *Pliaglis (NDA 021717)*
    - *Synera (NDA 021623)*
    - *Kovanaze (NDA 208032)"*

***Reviewer's note:*** No data from above listed drugs/NDAs were used to support the approval of the current NDA; all nonclinical elements of the support were provided by published literature or an extended, safe history of clinical use. The current approved labeling for listed NDAs was used as a comparator to ensure harmony across the labeling for these drug products.

## 2.3 Drug Formulation

**Table 1. Formulation of Tetracaine Ophthalmic Solution, 0.5%**

| Component | Concentration (% w/v) | Function |
|---|---|---|
| Tetracaine hydrochloride | 0.5 | Active |
| Chlorobutanol | 0.4 | Preservative |
| Boric Acid | (b) (4) | |
| Edetate Disodium (b) (4) | | |
| Potassium chloride | | |
| HCl/NaOH | -as needed | pH adjustment |
| (b) (4) | | |

## 2.4 Comments on Novel Excipients

All excipients are qualified for topical ophthalmic use.

## 2.5 Comments on Impurities/Degradants of Concern

**Drug Substance/Product Related Impurities**

- No issues regarding impurities or qualification of impurities were found during review.

### 2.6 Proposed Clinical Population and Dosing Regimen

Tetracaine Hydrochloride Ophthalmic Solution USP, 0.5% is indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic. The dosing regimen is for “one drop topically in the eye(s), as needed” per Applicant’s proposed labeling.

The average reported drop volume was approximately 0.034 mL, therefore the total dose is 0.170 mg/drop or 0.340 mg/dose, if administered bilaterally.

### 2.7 Regulatory Background

The drug product, Tetracaine Hydrochloride Ophthalmic Solution 0.5% has been legally marketed in the United States by the Applicant since 1992 and by other manufacturers with an FDA status of "unapproved drug".

## 3 Studies Submitted

### 3.1 Studies Reviewed


- Grant, R., and D. Acosta, 1994, “A digitized fluorescence imaging study on the effects of local anesthetics on cytosolic calcium and mitochondrial membrane potential in cultured rabbit corneal epithelial cells”, *Toxicol Appl Pharmacol*, 129: 23 – 35.
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## 3.2 Studies Not Reviewed


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# 4 Pharmacology

## 4.1 Primary Pharmacology

No new pharmacology studies with tetracaine hydrochloride were conducted by the Applicant for this application. It is well established that when applied locally to nerve tissue in appropriate concentrations, tetracaine reversibly blocks action potentials that are typically responsible for nerve conduction. Tetracaine blocks conduction by decreasing or preventing the large transient increase in the permeability of the cell membrane to sodium ions that normally is produced during nerve signal propagation.

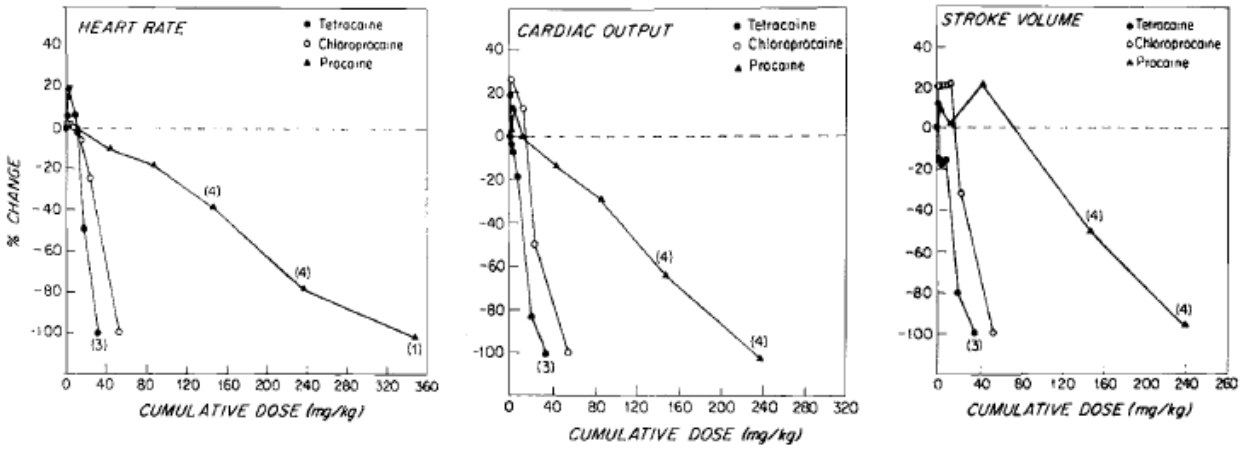
## 4.3 Safety Pharmacology

Safety pharmacology studies of tetracaine have not been conducted by the Applicant.

**Liu, P., *et al*., 1982, “Acute cardiovascular toxicity of procaine, chloroprocaine, and Tetracaine in anesthetized ventilated dogs”, *Regional Anesth*, 7: 14 -19.**

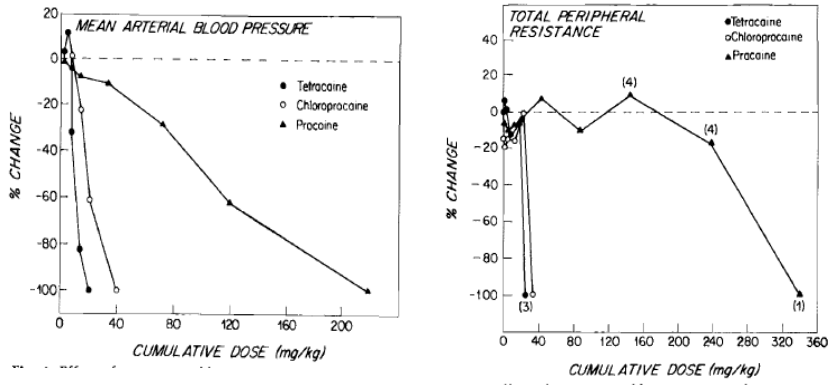
The acute intravenous cardiovascular toxicity of tetracaine was determined in pentobarbitalized, ventilated dogs (n=5). The cumulative lethal dose was approximately 30 mg/kg. Significant depression of mean arterial blood pressure, heart rate, cardiac output and stroke volume was observed at 10 mg/kg. A statistically significant decrease ($p < 0.01$) in heart rate was observed at a cumulative dose of 19 mg/kg of tetracaine (Figure 1). The authors state that an initial increase in cardiac output and stroke volume of ~20% was seen with low doses. The actual doses which caused these increases were not defined, and these increases were not statistically significant. Statistically significant decreases ($p < 0.01$) in cardiac output and stroke volume occurred at 19 mg/kg of tetracaine.

**Figure 1. Effect of tetracaine on cardiovascular parameters**



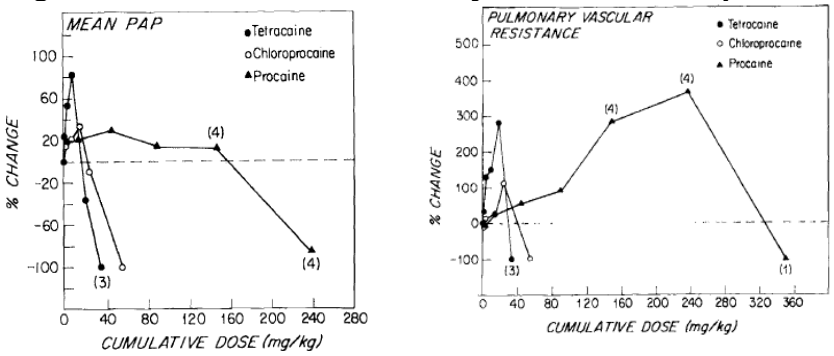

Statistically significant hypotension occurred at doses of 9 mg/kg of tetracaine ($p < 0.01$) (Figure 2). No significant change in total peripheral resistance was observed until the lethal dose was reached.

**Figure 2. Effect of tetracaine hydrochloride on vascular parameters**




Tetracaine produced a rise in both mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR; Fig. 3). The increase in PAP achieved statistical significance ($p < 0.01$) at a dose of 9 mg/kg. The authors state that peak increases in PVR of 279% were observed, but the dose which caused the effect was not defined (see Figure 3, below). A decrease in both parameters occurred only at the lethal dose.

**Figure 3. Effect of tetracaine hydrochloride on pulmonary parameters**




**Reviewer's note:** The total dose of 0.170 mg/eye/day or 0.340 mg/day total daily dose if administered bilaterally. The lowest dose of tetracaine which cause systemic cardiovascular or pulmonary effects in the dog was 9 mg/kg which represents a ~860-fold margin based on body surface are a (mg/m$^2$ basis) over 100% absorption of the recommended human ophthalmic dose (bilateral administration; presuming only a single drop per eye is administered to the patient).

**Liu, P., *et al*., 1983, "Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and Tetracaine in awake dogs following rapid intravenous administration", *Anesth Analg*, 62: 375 – 379.**

The toxicity of tetracaine was reported in awake dogs following rapid intravenous administration. Each animal received increasing serial intravenous doses of tetracaine at 30-min intervals. The dosing schedule of 1.0, 3.0, 5.0, 10.0, and 15.0 mg/kg was terminated when frank seizure activity was observed. Additionally, animals were continuously observed for other signs of overt systemic effects such as tremor, salivation, sedation, muscular rigidity, and death. A mean dose of approximately 3 mg/kg tetracaine caused convulsions. The duration of convulsive activity was 5.2 ± 2.0 min. One animal which received 4 mg/kg tetracaine continued to convulse for 15 minutes, showed signs of respiratory and cardiac depression and ultimately died. The mean dose which caused irreversible cardiovascular depression and death was 26.9 mg/kg. The ratio of the convulsive dose to the dose causing cardiovascular depression was 6.7 indicating that the CNS is more sensitive to tetracaine toxicity than the cardiovascular system.

**Reviewer's note:** The dose which caused convulsions, 3 mg/kg, is approximately 290-fold higher than 100% absorption of the recommended human ophthalmic dose (bilateral administration; presuming only a single drop per eye is administered to the patient), on a mg/m$^2$ basis.

# 5 Pharmacokinetics/ADME/Toxicokinetics

## 5.1 PK/ADME

**Absorption**

**Igarashi, H., 1984, "Studies on rabbit corneal permeability of local anesthetics (I)", *Japan J Pharmacol*, 34: 429 – 434.**

Corneal permeability velocity and hydration rate (corneal swelling) of tetracaine and other ester local anesthetics was determined in the rabbit. Albino rabbit eyes were isolated and the sclera excised along the external margin 2-3 mm from the corneal outline and placed in the center of a corneal permeability experimental chamber. Samples of cocaine·HCL, procaine·HCI and tetracaine·HCI were prepared at concentrations of 0.25. 0.5 and 1% dissolved in an artificial tear solution. This solution and artificial aqueous humor solution were placed into the tear side and aqueous humor side of the chamber, respectively. After specified incubation times, the volumes of solutions on both sides of the chamber were measured. In addition, the amount of anesthetic on the aqueous humor side and the residual quantity on the tear side were also measured. For the determination of corneal hydration, the wet weight of only the corneal permeable area (7 mm in diameter) was determined immediately after excision from the sclera-corneal specimen and removal of surface water on the cornea after incubation.

Compared to cocaine and procaine, tetracaine demonstrated the lowest permeability and highest hydration rate. Permeability appeared to be a passive process and was indirectly proportional to molecule size when compared to other ester local anesthetics.

# 6 General Toxicology

No single or repeat dose general toxicology studies were conducted or referenced by the Applicant.

# 7 Genetic Toxicology

No genetic toxicology studies were conducted or referenced by the Applicant.

# 8 Carcinogenicity

No carcinogenicity studies were conducted or referenced by the Applicant.

# 9 Reproductive and Developmental Toxicology

No reproductive and developmental toxicity studies were conducted or referenced by the Applicant.

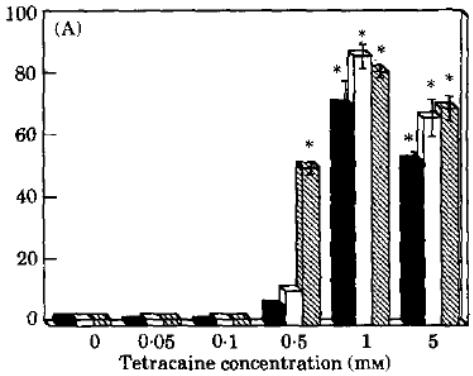
# 10 Special Toxicology Studies

### 10.1 Ocular toxicity

**Grant, R., and D. Acosta, 1994, "Comparative toxicity of tetracaine, proparacaine, and cocaine evaluated with primary cultures of rabbit corneal epithelial cells", *Exp Eye Res*, 58: 469 – 478.**

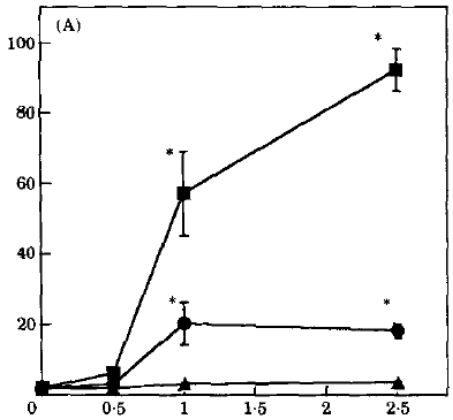
This study examined the cytotoxicity of tetracaine in primary cultures of rabbit corneal epithelial cells. A lactate dehydrogenase leakage test was utilized to determine the effect of tetracaine on cell viability. The amount of LDH leakage of treated cells was compared to total cellular LDH and was expressed as a percentage of total cellular LDH following incubation for 4 (■), 8 (□) or 24 (▨) hours.

**Figure 4. Cell viability of primary rabbit corneal cells following extended culture in presence of tetracaine**



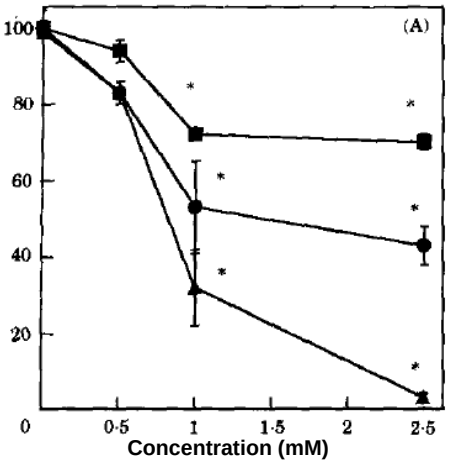

In another experiment, a time and dose dependent effect on cell viability was demonstrated following 15 (▲), 60 (●) or 120 (■) minutes of incubation. Tetracaine was reported with an $EC_{50}$ = 0.96 mM for cytotoxicity following 120 minutes of incubation.

**Figure 5. Cell viability of primary rabbit corneal cells following short-term culture in presence of tetracaine**



A time and dose dependent effect on mitochondrial integrity was demonstrated following 15 (■), 60 (●) or 120 (▲) minutes of incubation with tetracaine. A mitochondrial reduction assay resulted in $EC_{50}$ = 0.81 mM following 120 minutes of incubation.

**Figure 6. Mitochondrial membrane potential in primary rabbit corneal cells following incubation with tetracaine**




**Gunderson, T. and S. Liebman, 1944, "Effect of local anesthetics on regeneration of corneal epithelium", *Arch Ophthalmol*, 31: 29 – 33.**

This study determined the effects of tetracaine (0.5% containing 0.5% chlorobutanol) in hypotonic, isotonic and hypertonic solutions on the regeneration of corneal epithelium in guinea pigs following corneal injury (abrasion). Treatment with tetracaine was performed hourly until the lesion showed no fluorescein staining, a sign of complete regeneration. Whereas control eyes regenerated within 44 hours of abrasion, tetracaine delayed regeneration to 68 hours when in iso- or hypertonic solutions and up to 92 hours in hypotonic solution.

**Judge, A., *et al*., 1997, "Corneal endothelial toxicity of topical anesthesia", *Ophthalmology*, 104(9): 1373 – 1379.**

This study determined the corneal endothelial toxicity of tetracaine (0.5%) in pigmented rabbits. Corneal thickness and clarity were measured and the toxicity of tetracaine was statistically indistinguishable from balanced salt solution, although mild toxicity was suggested by clinical observation of decreased clarity.

**Patton, T. and J. Robinson, 1975, "Influence of topical anesthesia on tear dynamics and ocular drug bioavailability in albino rabbits", *J Pharm Sci*, 64: 267 – 271.**

The bioavailability of topically applied tetracaine on tear production and instilled solution drainage was determined. Male albino rabbits received a drop of tetracaine (0.5%) in the test eye or a drop of normal saline in the contralateral eye as control. Determination of lacrimal turnover rate and instilled solution drainage rate was determined using a radioactive technetium tracer. Tear secretion was determined using Schirmer strips.

Tetracaine hydrochloride caused a significant, dose-dependent decrease in the normal turnover rate of the lacrimal fluid, indicating decreased tear production (Table 2). Tetracaine caused significant reductions in tear production up to 70%, as shown by secretion tests.

**Table 2. Turnover rate of instilled volume of technetium (25 µL) in rabbits following various doses of tetracaine**

| Number of drops instilled | Turnover rate (µL/min) |
|---|---|
| 0 | 0.66 |
| 1 | 0.20 |
| 2 | 0.19 |
| 3 | 0.13 |
| 4 | 0.11 |
| 5 | 0.10 |

Tetracaine hydrochloride caused a dose-dependent reduction in the drainage rate of an instilled solution (Table 3).

**Table 3. Drainage rate constants of lacrimal fluid in rabbits following various doses of tetracaine**

| Number of drops instilled | Drainage rate ($min^{-1}$) |
|---|---|
| 0 | 0.54 |
| 1 | 0.39 |
| 2 | 0.35 |
| 3 | 0.42 |
| 4 | 0.12 |
| 5 | 0.06 |

**Pfister, R. and N. Burstein, 1976, "The effects of ophthalmic drugs, vehicles, and preservatives on corneal epithelium", *Invest Ophthalmol*, 15(4): 246 – 259.**

In this study performed in New Zealand White rabbits, a single dose of tetracaine (0.5%) did not have a significant effect on corneal surface microvilli when examined by scanning electron microscopy. Tetracaine had little or no effect on cell junctions, plasma membrane structure or epithelial organization.

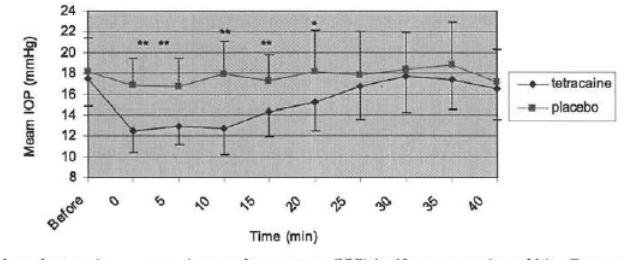
**Sarchahi, A. and H. Bozorgi, 2012, "Effect of tetracaine on intraocular pressure in normal and hypertensive rabbit eyes", *J Ophthalmic Vis Res*, 7: 29 – 33.**

The study was conducted on 12 healthy rabbits as controls and 6 healthy rabbits in which an experimental model of ocular hypertension (OHT) was induced by administration of 70 mL/kg of tap water through an orogastric tube. One drop of tetracaine 0.5% was instilled in the left eye, while a drop of normal saline (placebo) was applied to the right eye, with the instillation of drops repeated after 55 minutes. IOP was measured before and at specific times after drop administration.

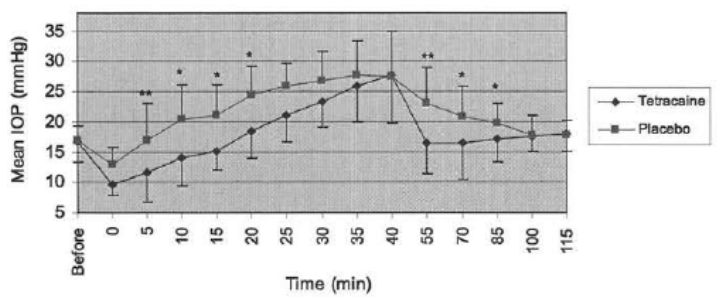
Tetracaine treated eyes in both groups (ocular hypertensive and normal controls) demonstrated significant IOP reduction at time zero (immediately after drop instillation) which was sustained up to 20 minutes, as compared to placebo treated eyes ($P<0.05$). In ocular hypertensive rabbits, repeat instillation of tetracaine at 55 minutes significantly reduced IOP immediately and up to 30 minutes thereafter.

**Figure 7. Effect of tetracaine on intraocular pressure in normal and hypotensive eyes**

Normal:




Hypertensive



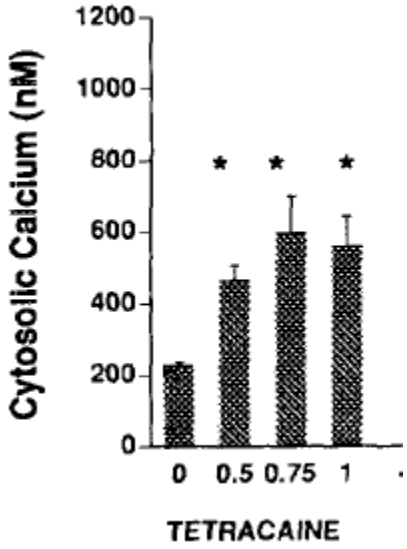

**10.2 Molecular mechanisms of toxicity**

**Grant, R., and D. Acosta, 1994, "A digitized fluorescence imaging study on the effects of local anesthetics on cytosolic calcium and mitochondrial membrane potential in cultured rabbit corneal epithelial cells", *Toxicol Appl Pharmacol*, 129: 23 – 35.**

This study evaluated the effects of tetracaine on cytosolic calcium and mitochondrial membrane potential in primary cultures of rabbit corneal epithelial cells. The cells were treated for 15 min with tetracaine (0.5-2.5 mM) and changes in intracellular calcium [Ca2+]i and mitochondrial membrane potential were examined.

A dose-dependent increase in [Ca2+]i was evident after treatment with tetracaine.

**Figure 8. Intracellular calcium concentration of rabbit corneal cells following incubation with tetracaine**




Concentrations ≥ 2.5 mM tetracaine dissipated mitochondrial membrane potential (ΔΨ). A rise in [Ca2+]i preceded any loss of ΔΨ caused by TTC. The authors conclude that tetracaine elevates intracellular calcium which may contribute to disruption of the mitochondrial membrane causing loss of potential and cytotoxicity.

**Higbee, R., and L. Hazlett, 1989, "Topical ocular anesthetics affect epithelial cytoskeletal proteins of wounded cornea", *J Ocul Pharmacol*, 5(3): 241 – 253.**

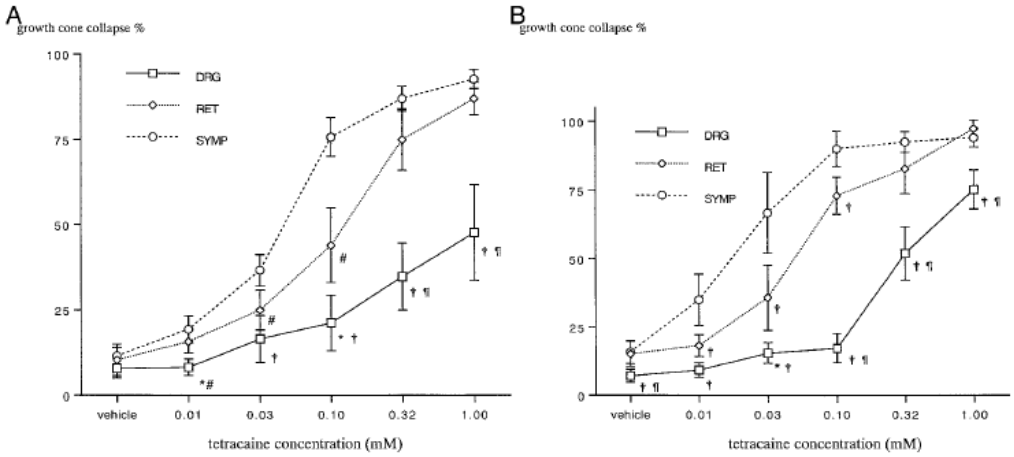
This study investigated cytoskeletal dynamics of actin, myosin and calmodulin in injured corneal cells following exposure to tetracaine (0.5%). Following injury (trephine abrasion and n-heptanol treatment), the corneal cells of Swiss mice were exposed to tetracaine in vitro. Whereas control cells closed the wound within 24 hours, corneas exposed to tetracaine failed to close. Immunostaining for actin, myosin and calmodulin was enhanced in basal and superficial cells closest to the leading edge of the wound in untreated cells whereas treatment with tetracaine diminished immunostaining suggesting decreased cell migration and rearrangement.

**Saito, S., *et al*., 2001, "Direct neurotoxicity of tetracaine on growth cones and neurites of growing neurons in vitro", *Anesthesiology*, 95: 726 – 733.**

This study examined the effect of tetracaine on neuron morphology and nerve regeneration. Three different neuronal tissues (dorsal root ganglion, retinal ganglion cell layer, and sympathetic ganglion chain) were isolated from an age-matched chick embryo and the effects of tetracaine were examined microscopically and by a quantitative morphologic assay, the growth cone collapse assay.

Tetracaine induced growth cone collapse and neurite destruction. The three neuronal tissues showed a significantly different dose-response, both at 60 min and at 24 h after the application of tetracaine ($p < 0.01$). The $ED_{50}$ values at 60 min were 1.53 mM in dorsal root ganglion (DRG), 0.15 mM in retinal (RET), and 0.06 mM in sympathetic ganglion chain (SYMP) cultures. The $ED_{50}$ values at 24 h were 0.43 mM in dorsal root ganglion, 0.07 mM in retinal, and 0.02 mM in sympathetic ganglion chain cultures. Concentration of nerve growth factor in the culture media did not influence the $ED_{50}$ values.

**Figure 9. Percent growth cone collapse of neuronal tissue following exposure to tetracaine**




The growth cone collapsing effect was partially reversible in dorsal root ganglion and retinal neurons. However, in the sympathetic ganglion culture, no reversibility was observed after exposure to 1 mM tetracaine for 10 or for 60 min.

# 11 Integrated Summary and Safety Evaluation

The NDA is approvable from a Pharmacology/Toxicology perspective. Publications submitted by the Applicant show cardiovascular and CNS effects at high systemic doses of tetracaine (not clinically relevant), and some ocular effects following topical instillation at clinically relevant doses, including a temporary decrease in intraocular pressure and reduced tear production and turnover.

As a 505(b)(2) NDA application, a long history of pre-approval topical ophthalmic use in the patient population indicated adequately characterizes the safety profile of this formulation of tetracaine administered via topical ophthalmic drop.

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/s/
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AARON M RUHLAND
11/09/2018

ANDREW J MCDOUGAL on behalf of LORI E KOTCH
11/09/2018