# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208135Orig1s000

# CROSS DISCIPLINE TEAM LEADER REVIEW

# Cross-Discipline Team Leader Review for NDA 208135

| | |
|---|---|
| **Date** | February 26, 2016 |
| **From** | William M. Boyd, M.D. |
| **Subject** | Cross-Discipline Team Leader Review |
| **NDA #** | 208135 |
| **Applicant** | Alcon Research, Ltd. |
| **Date of Submission** | April 30, 2015 |
| **PDUFA Goal Date** | February 29, 2016 |
| **Type of Application** | 505(b)(2) |
| **Name** | Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT® |
| **Dosage forms / Strength** | Topical ophthalmic solution |
| **Proposed Indication(s)** | Indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic |
| **Recommended:** | Recommended for Approval |

## 1. Introduction

Tetracaine has been commercially available as an ophthalmic solution from several manufacturers in the United States for over 45 years for use as a topical anesthetic in ophthalmologic procedures. (b) (4) A non-ophthalmic topical anesthetic spray of tetracaine was submitted in 1963, approved in 1965, and withdrawn in 1985 (NDA 14-766). The active ingredient is currently approved for marketing for two dermatologic products (NDA 21-717 and NDA 21-623)

Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT is a sterile, preservative free formulation of tetracaine, currently marketed as an unapproved drug in the United States by Alcon, Inc., and has been sold in the US for at least 30 years. It is indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic. Tetracaine is purported to induce local anesthesia by reversibly blocking conduction through nerve fibers by decreasing or preventing transient increases in the permeability of the membrane to sodium ions. This is believed to occur via binding of the drug to voltage-gated sodium channels inside the membrane.

This is a 505(b)(2) application referencing published literature.

## 2. Background

The primary support for efficacy for tetracaine hydrochloride ophthalmic solution 0.5% includes three (3) literature reports of controlled, prospective studies evaluating the efficacy of tetracaine 0.5% in providing anesthesia for ophthalmic procedures. In these 3 studies, tetracaine 0.5% demonstrates clinical effectiveness for the indication being sought in providing anesthesia for various ophthalmic procedures including refractive surgery, intravitreal injection and tonometry.

A pre-IND meeting (PIND 115866) was held with the Agency for this product in April 2013. It was agreed that published literature reports were likely sufficient for NDA submission.

**Currently Available Treatments (Approved Drugs) for Proposed Indications**

| Tradename | Established Name | NDA Number | Indication |
|---|---|---|---|
| Multiple | Proparacaine 0.5% | ANDA 80027<br>ANDA 40277<br>ANDA 87681<br>ANDA 40074 | Indicated for topical anesthesia in ophthalmic practice. Representative ophthalmic procedures in which the preparation provides good local anesthesia include measurement of intraocular pressure (tonometry), removal of foreign bodies and sutures from the cornea, conjunctival scraping in diagnosis and gonioscopic examination; it is also indicated for use as a topical anesthetic prior to surgical operations such as cataract extraction. |
| Akten | Lidocaine 3.5% | NDA 022221 | Local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures |

In their 2/17/2016 submission (SDN012), Alcon states that the sources it usually uses to estimate total use of a class of products, e.g., IMS, track prescriptions and do not report in-office use. Therefore, the following is a very rough approximation of the market share of Alcon Tetracaine SteriUnits. In 2015, Alcon sold approximately (b) (4) units in the US (See Table 1 below). This number has gradually increased since 2001 when the number of units was less than (b) (4). Annually, approximately (b) (4) cataract surgeries and approximately (b) (4) other in-office procedures that require topical anesthesia are performed in the US.

**Table 1 Unit sales data for tetracaine SteriUnits 2000-2015**

| Sales Quantity | (b) (4) |
|---|---|
| Caribbean | |
| Kuwait/Private | |
| Puerto Rico | |
| Sweden | |
| Thailand | |
| Unknown Market | |
| US Cat. Products | |
| TOTAL | |
| | |
| Sales Quantity | |
| Caribbean | |
| Kuwait/Private | |
| Puerto Rico | |
| Sweden | |
| Thailand | |
| Unknown Market | |
| US Cat. Products | |
| TOTAL | |

# 3. CMC

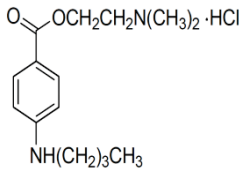
**DRUG SUBSTANCE:**

## Nomenclature

| | |
|---|---|
| USAN/INN name: | Tetracaine Hydrochloride |
| Chemical names: | Benzoic acid, 4-(butylamino)-, 2-(dimethylamino)ethyl ester, monohydrochloride (IUPAC)<br><br>2-(Dimethylamino)ethyl *p*-(butylamino)benzoate monohydrochloride (IUPAC)<br><br>Benzoic acid, 4-(butylamino)-, 2-(dimethylamino)ethyl ester, monohydrochloride (CAS) |
| Company/laboratory code: | AL-15154A |
| Other non-proprietary names: | CAS Registry No.: 136-47-0 |

## Structure

Structural formula:




| | |
|---|---|
| Molecular formula: | $C_{15}H_{24}N_2O_2 \cdot HCl$ |
| Molecular weight: | 300.82 (HCl salt) |

(b) (4)

Tetracaine hydrochloride is a well-known and well characterized drug substance and is described in the USP and Ph. Eur.

Tetracaine hydrochloride is manufactured and tested by: (b) (4)

Information concerning the proof of structure and physicochemical characterization of tetracaine hydrochloride has been described by (b) (4) in DMF (b) (4). Alcon has compared tetracaine hydrochloride from (b) (4) to the USP Reference Standard to demonstrate that the material has the correct structure.

Alcon has confirmed the molecular formula by elemental analysis. IR, UV, $^{1}H$ and $^{13}C$ NMR and mass spectra are consistent with the proposed structure.

**Tests and Specifications for Tetracaine Hydrochloride Drug Substance**

| Test | Method | Acceptance criteria |
|---|---|---|
| Identification (IR) | FWMDOC-02925 | Conforms to reference spectrum |
| Identification (UV) | USP monograph | Conforms to reference spectrum |
| Identification (melting point) | USP monograph | 130-132 °C |
| Identification (chloride) | USP monograph | Meets requirement for Chloride |
| Water | USP monograph | NMT (b) (4)% |
| Residue on Ignition | USP monograph | NMT %  |
| Chromatographic purity | USP monograph | Individual Impurity: NMT (b) (4)%<br>Total Impurities: NMT % |
| Assay | USP monograph | (b) (4)% (anhydrous) |
| Description | Alcon | Fine, white, crystalline powder; odorless |
| Residual solvents | FWMDOC-14396 | Complies with USP <467> |
| Related substances (HPLC) | Ph. Eur. monograph | Impurity (b) (4) NMT (b) (4)%<br>Impurity NMT (b) (4)%<br>Impurity NMT (b) (4)%<br>Any Single Impurity: NMT (b) (4)%<br>Total Impurities: NMT (b) (4)% |

**DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:**

**Table 3.2.P.1–1 Composition of Tetracaine Hydrochloride Ophthalmic Solution, 0.5% (FID 94152)**

| Component | Amount (% w/v) | Function/Purpose | Compendial Status |
|---|---|---|---|
| Tetracaine Hydrochloride | 0.5[a] (b) (4) | Active | USP |
| Sodium Acetate (Trihydrate) | (b) (4) | (b) (4) | USP |
| Sodium Chloride | | (b) (4) | USP |
| Acetic Acid (b) (4) | Target pH 4.5 | pH Adjustor | NF<br>USP |
| Water for Injection | (b) (4) | (b) (4) | USP |

[a] (b) (4)

## Impurities Degradation Products

The potential degradation products of tetracaine hydrochloride in the finished drug product are shown in Table 3.2.P.5.5-1 of the NDA submission.

**Table 3.2.P.5.5–1 Potential Degradation Products**

| Degradation Product | Structure | RRT |
|---|---|---|
| (b) (4) | | |

[a] Specified Impurities

All of the potential degradation products are routinely controlled in the finished drug product by the specific, stability-indicating, validated HPLC method. (b) (4) and (b) (4) are specified degradation products. (b) (4) are oxidation degradation products created by the (b) (4) and (b) (4) were identified by LC/MS and are the only degradation products observed at levels ≥ (b) (4)% in product stability studies up to 24 months. The other specified degradation products were seen at relatively low levels in product stability studies up to 24 months.

**CONTAINER CLOSURE SYSTEM:**

The package system selected for tetracaine hydrochloride ophthalmic solution,0.5% is comprised of a natural medium density polyethylene (b) (4) round bottle with a natural low density polyethylene (LDPE) dispensing plug and a white polypropylene (PP) closure enclosed in a polyvinylidene chloride (PVC) blister with heat sealed Tyvek backing.

The primary packaging component materials information is summarized in the table below. The bottle and plug components will be (b) (4), and the closure will be (b) (4). The filled bottle with plug and closure are sealed into the blister (b) (4). Tamper evidence is provided by the heat sealed Tyvek backing on the blister.

Table 2.3.P.7–1 Primary Packaging Materials and Components

| Component | Component Material | Resin Suppliers | Material DMF[a] |
|---|---|---|---|
| Round Bottle | Medium Density Polyethylene | (b) (4) | (b) (4) |
| Dispensing Plug | Low Density Polyethylene | | |
| Closure | Polypropylene | | |
| Label | (b) (4) | Not Applicable | Not applicable |
| Blister | PVC[c] | Not Applicable | Not applicable |
| Backing | Tyvek (b) (4) | Not Applicable | Not applicable |

a Letters of Authorization to reference the DMFs listed are provided.
b Low Density Polyethylene
c High Density Polyethylene
d Polypropylene

A drop size study was conducted to simulate patient use of tetracaine hydrochloride ophthalmic solution, 0.5%. The data indicate an average drop size of 38.3µl with a standard deviation of 3.3 µl.

**PROPOSED REGULATORY SPECIFICATIONS:**

| Test | Specification |
|---|---|
| Tetracaine Hydrochloride Identity (HPLC)[a] | Positive |
| Tetracaine Hydrochloride Identity (TLC)[b] | Positive |
| Tetracaine Hydrochloride Identity (HPLC) | 90-110% label |
| Tetracaine Hydrochloride Identity (HPLC)[b]<br>(b) (4)<br><br><br><br>Any Single Unspecified Impurity[c]<br>Total Impurities | <br>NMT (b) (4)% of Active<br>(b) (4)% of Active<br>NMT (b) (4)% of Active<br>NMT % of Active<br>NMT % of Active<br>NMT (b) (4)% of Active |
| pH (Potentiometric) | |
| Osmolality (Freezing Point Depression) | (b) (4)mOsm/kg |
| Appearance (Visual):<br>Color<br>Clarity<br>Precipitate | <br>(b) (4)<br>NMT Ph. Eur. II<br>None |
| Particulate Matter by HIAC | Meets USP Requirements<br>NMT (b) (4)particles/m (b) (4)<br>NMT (b) (4)particles/mL<br>NMT particles/mL |
| Sterility, Contents[d] | Meets USP Requirements |
| Sterility, Exteriors[d] | Meets USP Requirements |

[a] Release Test only
[b] Report any impurity > (b) (4)% of active
[c] (b) (4) are included under Any Single Unspecified Impurity
[d] Sterility testing will not be routinely conducted on production lots except at release. However, if tested, samples will comply with USP requirements. Sterility (contents and exterior) testing will also be performed at expiry for any commercial lots placed on stability.
NMT=Not more than
LT=Less than

From the OPQ Integrated Quality Assessment Review dated 1/25/2016, page 5:

> The drug product specifications include tests for two (b) (4) that are controlled at NMT (b) (4)% and (b) (4)%. The total impurity, as a result is controlled at NMT (b) (4)%. These limits are based on the batch release and stability data provided in the NDA. CMC consulted with Pharm/Tox on these impurities and Pharm/Tox reviewer confirmed that these impurities and the (b) (4) (a drug substance degradent controlled at NMT (b) (4)% in the drug product specifications) are not qualified at the proposed limits. In their review, the Pharm/Tox deferred to CMC and clinical on the acceptability of the proposed limits. Upon repeated requests to provide impurity profile for historical commercial batches, the applicant indicated that these impurities and (b) (4) impurities were not tested in the past. The applicant indicated that no changes to the manufacturing process were made since 1996 (TCON dated January 21, 2016 and follow-up email dated January 22, 2016). Based on this information, it may be concluded that impurity profile in the proposed product will be the same or similar to the

Tetracaine Hydrochloride Ophthalmic Solution 0.5% currently marketed by the applicant. ***However, the safety of the impurity at the proposed levels should be assessed by the clinical and nonclinical divisions***. See Section 7 of this CDTL Review.

**FACILITIES INSPECTIONS**:

The facilities supporting manufacturing of drug substance and drug product for tetracaine hydrochloride ophthalmic solution 0.5%, NDA 208135, are assessed to be acceptable as of 01/16/2016.

**DRUG SUBSTANCE**

| Facility Name | FEI | Recommended Profile Code | Responsibilities | Facility Sub-Score | Process Sub-Score | Product Sub-Score | Overall Initial Facility Risk Assessment | Recommendation |
|---|---|---|---|---|---|---|---|---|
| (b) (4) | | CSN | Drug substance manufacturing and testing per DMF# (b) (4) | 1 | 6 | 0 | 7 | Waive Inspection; recommend approval at current time |

| Establishment Name | FEI Number | Responsibilities and Profile Codes | Initial Risks Identified | Current Status | Final Recommendation |
|---|---|---|---|---|---|
| (b) (4) | (b) (4) | **CSN**-Drug substance manufacturing and testing per DMF# (b) (4) | None | Last inspection (b) (4) for profile code CSN with a status of NAI.<br><br>Recommendation: Waive Inspection - Acceptable based on history/profile (as of 06/02/2015) | Acceptable as of 12/11/2015. |

**DRUG PRODUCT**

| Facility Name | FEI | Recommended Profile Code | Responsibilities | Facility Sub-Score | Process Sub-Score | Product Sub-Score | Overall Initial Facility Risk Assessment | Recommendation |
|---|---|---|---|---|---|---|---|---|
| Alcon Research Ltd. | 1610287 | SLQ | Drug product manufacturing, packaging, testing, stability | 16 | 15 | 0 | 31 | Waive Inspection; sent for DO file review |
| (b) (4) | (b) (4) | | (b) (4) | 1 | 28 | 0 | 29 | Assigned Inspection |

| Establishment Name | FEI Number | Responsibilities and Profile Codes | Initial Risks Identified | Current Status | Final Recommendation |
|---|---|---|---|---|---|
| Alcon Research Ltd. | 1610287 | SLQ-Drug product manufacturing, testing and stability | Process validation of sterilization operations in (b) (4) Blister packaging integrity and its ability to hold up to the (b) (4) sterilization are areas worth reviewing closely. | Last inspection 05/01/2014 for profile code SLQ with a status of NAI.<br><br>Recommendation: Waive Inspection - Acceptable based on history/profile and DO Recommendation | Acceptable as of 12/11/2015 |

| Establishment Name | FEI Number | Responsibilities and Profile Codes | Initial Risks Identified | Current Status | Final Recommendation |
|---|---|---|---|---|---|
| (b) (4) | (b) (4) | (b) (4) Finished drug product (b) (4) sterilizer | Process related impurities/ degradents arise from (b) (4) sterilizatio dequate validation and monitoring (control on exposure of drug product to the (b) (4) needed for product quality | Last inspection Assign inspection<br><br>Recommendation: Acceptable based on inspection and DO Recommendation | Acceptable as of 12/11/2015 |

# 4. 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.

Regarding product-related impurities and (b) (4), two impurities identified by the applicant are proposed at specifications which exceed those recommended in ICH Q3B(R2). (b) (4) (b) (4) and (b) (4) are proposed at no more than (b) (4)% and (b) (4)%, respectively. There were no nonclinical data submitted to qualify these impurities above ICH recommended concentrations. The applicant stated that the formulation, manufacturing process, including key process parameters and controls for (b) (4) of blister packs for the proposed drug product are the same as those of the historically marketed commercial product.Only limited historical data regarding content of the proposed impurities in previously marketed clinical batches was provided because the previous assay did not clearly identify these impurities. An assessment of comparability of Tetracaine hydrochloride ophthalmic solution 0.5% to the historically marketed commercial product is deferred to the CMC team, and an assessment of the adequacy of the historic clinical data to support safety is deferred to the Clinical team.

The applicant has proposed drug product acceptance limits for (b) (4) The maximum total daily intake of these impurities falls below limits set in the (b) (4) and ocular safety of proposed acceptance limits is characterized in the published articles cited. Moreover, testing of historically marketed batches showed (b) (4) and (b) (4) concentrations which reasonably approximate the acceptance limits. No adverse events have been reported with Tetracaine Ophthalmic Solution 0.5% which were attributable to the (b) (4) (b) (4) within the drug product.

See Section 7 of this CDTL Review.

## 5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review dated 10/13/2015:

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 reviewer grants 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.

## 6. Sterility Assurance

From the OPQ Integrated Quality Assessment Review dated 1/25/2016:

The Alcon DROPTAINER® packaging system for the subject drug product consists of the following:

| Component | Description |
|---|---|
| Bottle | Natural medium density polyethylene (b) (4) (b) (4) round bottle, 4 mL |
| Dispensing Plug | Natural low density polyethylene (LDPE) dispensing plug |
| Closure | White polypropylene (PP) closure |

The bottle and plug are (b) (4) sterilized by (b) (4) (LOA for DMF (b) (4) provided), and the closure is sterilized by (b) (4) (LOA for DMF (b) (4) provided). The primary container/closure (C/C) system is enclosed in a polyvinylidene chloride (PVC) blister with heat sealed Tyvek backing. This sterile, blister packed product is the STERI-UNIT® configuration.

The overall Microbiological assessment is acceptable. Approval is recommended.

# 7. Clinical/Statistical - Efficacy

From the Medical Officer Review dated 1/20/16:

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. Specifically, the reports were reviewed to determine if tetracaine 0.5% was used in the trial; if the comparator arm was an approved product or not; if tetracaine was able to show superiority to the control arm or if tetracaine appeared to be equivalent to the control arm if it was an approved product. After a preliminary review of the original submission was complete, the Applicant was asked to provide additional support for the proposed indication. In addition, the Agency performed additional literature searches for the use of tetracaine 0.5% in topical ophthalmic anesthesia.

| Study | Design | Objective | Subjects | Treatment | Alcon Product |
|---|---|---|---|---|---|
| **Listing of Published Clinical Efficacy Studies of Tetracaine in Adults Provided by the Applicant** | | | | | |
| 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<br>1 drop of 0.5% tetracaine | unknown |
| (b) (4) | | | | | |
| 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<br>1 drop of 1% amethocaine* 5 min apart × 3 in fellow eye | No (1% solution) |
| (b) (4) | | | | | |
| 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<br>1 drop of 0.5% tetracaine 5 min apart × 3 | unknown |
| **Listing of Published Clinical Efficacy Studies of Tetracaine in Pediatric Patients Provided by the Applicant** | | | | | |
| Watson 1991 | Randomize, 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) |
| Carden 1998 | Randomize, controlled, | To test the effect of amethocaine on reducing | 62 (6 mos–15 years) | 2 drops of 0.5% amethocaine*, subconjunctival bupivacaine | Unknown |

| | | | | | |
|---|---|---|---|---|---|
| | observer masked | postoperative pain, vomiting, and length of stay in children having strabismus repair | | 0.5%, or placebo (saline) | |
| Kim 2003 | Randomize, 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 |
| Anninger 2007 | Randomize, 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) |
| **Additional literature reports submitted by the applicant during the review cycle to support the efficacy of tetracaine 0.5%** | | | | | |
| 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%<br>Proparacaine 0.5% | Yes |
| Rifkin 2012 | prospective, randomized | to determine factors associated with patients comfort during routine in-office intravitreal injection. | 60 | Proparacaine 0.5%<br>TetraVisc<br>Tetracaine 0.5% | Tetravisc (Cynacon/Ocusoft)<br>Tetracaine (Alcon) |
| 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 |
| 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><br>Lidocaine 5% | Unknown |
| Sabermoghadam 2012 | pilot study | to find a new form of lidocaine to give a sufficient level of anesthesia | 30 | Tetracaine<br><br>Lidocaine cyclodextrin | unknown |
| **Additional published article provided by the Agency** | | | | | |
| 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%<br>tetracaine 0.5% | No (Ocusoft) |
| (b) (4) | | | | | |

* Tetracaine is also known as amethocaine and pontocaine.

## Analysis of Primary Endpoint(s)

### Primary Sources of Efficacy

**Rifkin 2012**

This study was a prospective, randomized, single center study designed to determine factors associated with patients comfort during routine in-office intravitreal injection. Sixty (60) patients receiving intravitreal injections over 15 months for macular edema because of diabetes, age-related macular degeneration, or retinal vein occlusion were randomized to receive either tetracaine HCl 0.5% gel, proparacaine HCl or teracaine HCl ophthalmic solution before receiving intravitreal injections. A single drop was given 3 times over a 5-minute period. Each patient received at least 5 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. Patients who received less than 5 injections were excluded from the analysis. Fifteen (15) minutes after the intravitreal injection was given, patients were asked to rate the pain of injection from 0 (no pain/no distress) to 10 (agonizing pain/unbearable distress) using a Visual Analog Pain score survey.

The results were stratified by age, gender, diagnosis, injected eye, injection number, substance injected, needle gauge, and perception of visual acuity improvement from previous injection. Patients with any previous eye surgery other than routine and uncomplicated cataract surgery and diabetic patients with known peripheral neuropathy were excluded from the study. 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.

| Treatment | Mean Pain Score |
|---|---|
| tetracaine HCL 0.5% gel (N=100) | 3.39±2.26 |
| proparacaine HCL (N=100) | 3.17±2.18 |
| tetracaine HCL ophthalmic solution (N=100) | 3.05±2.01* |

*statistically significant difference **(p<0.01)** reported between tetracaine HCl ophthalmic solution and the other two treatment groups.

Subjects who received tetracaine ophthalmic solution reported the lowest pain score. The authors report that tetracaine is statistically superior to the comparator arms.

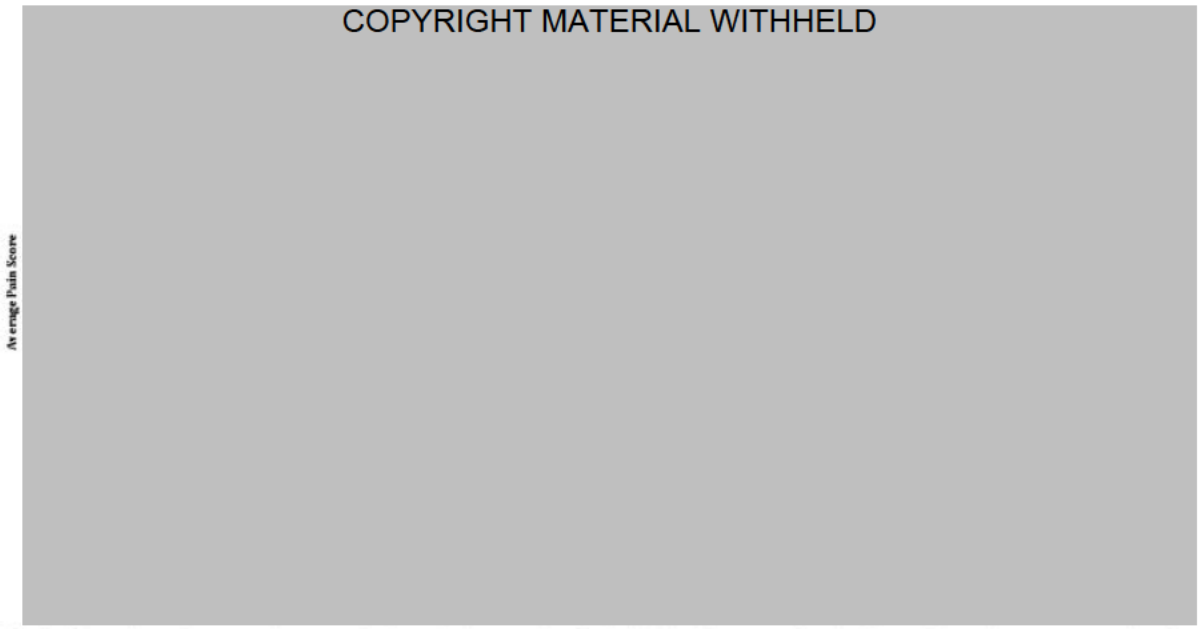



**Fig. 2.** Comparison of average pain scores of patients by demographics. Statistical significance was found with sex of the patient, age, perception of improvement of vision from previous injection and time of day of injection.


**Fig. 3.** Comparison of average pain scores with successive injection. Analysis of variance detected a statistically significant difference in pain score with each injection.

**Chalam 2009**

This study was designed to compare the clinical efficacy of lidocaine 2% with tetracaine 0.5% for cataract surgery. This was a randomized, multi-surgeon, controlled study in 122 cataract cases randomly assigned to receive lidocaine 2% or tetracaine 0.5% before clear corneal phacoemulsification. Subjects graded intra-operative pain using a visual analog scale (0-10) within 10 minutes of completion of surgery.


Tetracaine 0.5% was statistically superior to lidocaine 2% in pain control in preparation for clear corneal surgery.

**Moshirfar 2014**

This was a prospective, single-masked, randomized study of 256 eyes from 128 patients being treated with Lasik or PRK who received either tetracaine 0.5% in one eye and proparacaine in the other. Pain levels were graded on a 0-10 scale and were assessed upon instillation, during surgery, immediately postoperatively, 30 minutes postoperatively, overnight and on postoperative day 1. Patients were asked 30 minutes after surgery which anesthetic agent they would choose.

**Table 1** Patient demographics and treatment data

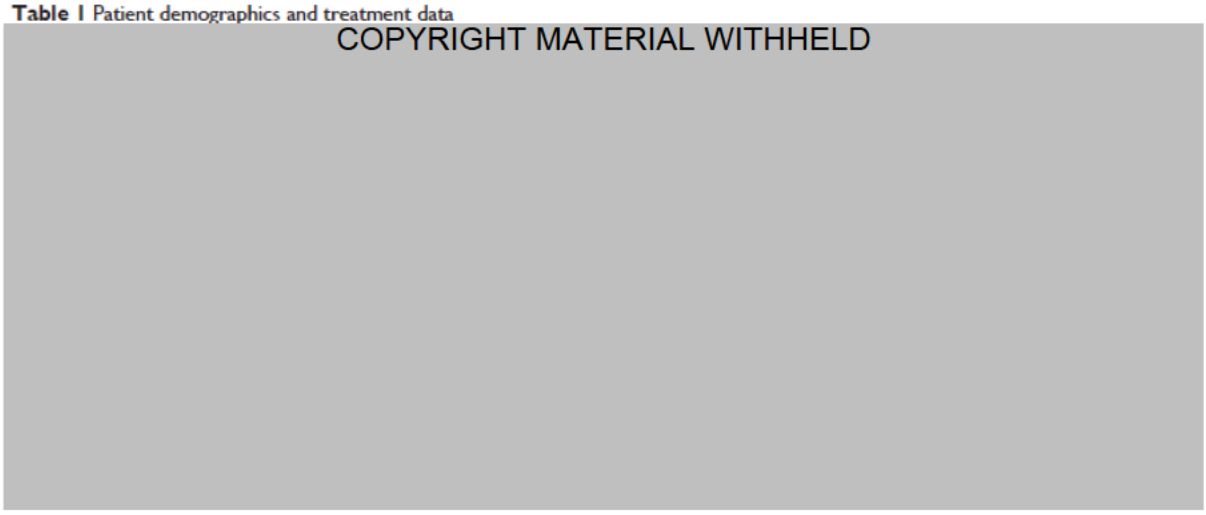


**Table 2** Pain outcomes: proparacaine versus tetracaine, graded 0 to 10



Tetracaine 0.5% appears to be clinically equivalent to proparacaine (approved product) in pain control during surgery and immediately postoperative in patients undergoing refractive surgery procedures. Tetracaine is statistically superior to proparacaine in pain 30 minutes postoperatively. Tetracaine causes more pain on instillation which is statistically significant in this trial.

(b) (4)

(b) (4)

**Shafi 1998**

This study was conducted to evaluate the claim that topical proxymetacaine produces little or no discomfort on instillation by comparing it against topical amethocaine. This was a randomized, masked, double masked prospective study involving 53 patients. Each patient received one drop of amethocaine 0.5% in one eye and one drop of proxymetacaine 0.5% in the other. The severity (0-4 point scale) and duration of discomfort for each topical anesthetic was assessed. To confirm proper instillation of the anesthetic drop, tonometry using a Tonopen was performed 5 minutes after drop instillation. 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.

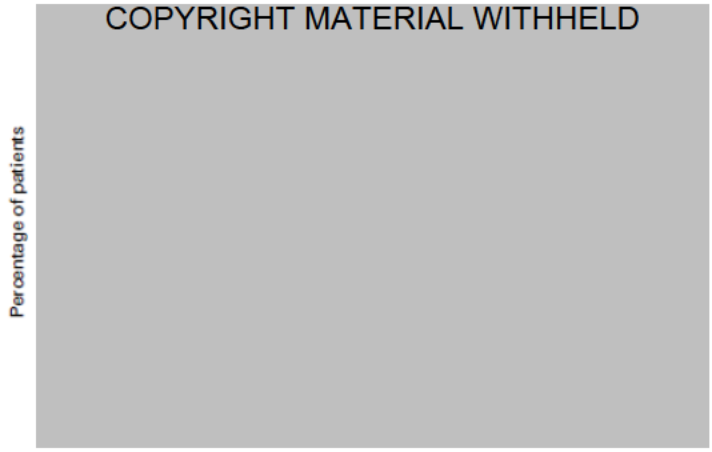



*Figure 2 Percentage of patients experiencing "no pain", "mild pain", "moderate pain", and "severe pain" as expressed on the descriptive discomfort scale.*

| | **Successful Tonometry** |
|---|---|
| Amethocaine 0.5% | 98% (n=52) |
| Proxymetacaine 0.5% | 93% (n=49) |
| p-value | 0.08 |

Note: Amethocaine is INN name for tetracaine
Proxymetacaine is INN name for proparacaine

Tetracaine 0.5% is clinically equivalent to proparacaine 0.5% in inducing anesthesia for tonometry.

**Additional Supportive Evidence Provided by the Applicant**

The additional articles provided by the Applicant do not provide direct evidence of the anesthetic effect of tetracaine 0.5% either because (1) the comparator used in the studies was not approved for the indication and tetracaine did not demonstrate superiority or (2) a higher dose of tetracaine was used in the study (i.e. 1%) or (3) the design of the trial was not adequate to determine the anesthetic effect of the drug.

However, several of the trials submitted by the Applicant that used lidocaine 2% as the comparator arm do provide supportive evidence of the anesthetic effect of tetracaine 0.5%. Lidocaine 3.5% which was approved in NDA 22-221 and reported in Busbee (2008) contains a trial that also evaluated the anesthetic effect of lidocaine 1.5% and 2.5%. Based on the results of this trial see (table 1), both the 1.5% and 2.5% formulations were statistically superior to placebo ($p<0.001$) for providing anesthetic effect and similar to the approved lidocaine 3.5%. It can be inferred that since 2% is bracketed by these two doses, it would be expected to provide the same effect; therefore, anesthetics that are equivalence to lidocaine 2% would be expected to be superior to placebo.

**Table 1 - Analysis of Primary Efficacy Endpoint-Clinical Trial 06AKO001 (ITT Population)**

| | Sham (N=54) | Lidocaine 1.5% (N=51) | Lidocaine 2.5% (N=52) | Lidocaine 3.5% (N=51) |
|---|---|---|---|---|
| Percent Achieving Anesthesia Within 5 Minutes of Dosing | 12 (22%) | 45 (88%) | 46 (89%) | 47 (92%) |
| P value | | <0.001 | <0.001 | <0.001 |

While all three trials are presented here for completeness, (b) (4) used tetracaine products from other manufacturers.

**Barequet 1999**
This study compared the efficacy of a single application of lidocaine 2% gel with tetracaine 0.5% drops for topical anesthesia in clear corneal cataract surgery in 25 eyes of 25 patients. Corneal sensation was measured with the Cochet-Bonnet aesthesiometer before application of the topical anesthesia, 5 minutes after application and at the conclusion of surgery.

| Treatment | Mean Corneal Sensation | | |
|---|---|---|---|
| | Pre-op | 5 min post drop | Post-op |
| Tetracaine 0.5% (N=13) | 6 | 0 | 0 |
| Lidocaine 2% (N=12) | 5 | 0 | 0 |

Scale (0-6)

Tetracaine and Lidocaine were effective in providing corneal anesthesia for clear corneal surgery.

(b) (4)

(b) (4)

## Efficacy Summary Statement

Multiple adequate and well controlled studies demonstrate the efficacy of tetracaine hydrochloride ophthalmic solution 0.5% in producing rapid and short-acting topical ophthalmic anesthesia. Topical administration of tetracaine hydrochloride ophthalmic solution 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.[1]

The primary support for efficacy for tetracaine hydrochloride ophthalmic solution 0.5% includes three (3) literature reports of controlled, prospective studies evaluating the efficacy of tetracaine 0.5% in providing anesthesia for ophthalmic procedures. In these 3 studies, tetracaine 0.5% is clinically equivalent to proparacaine which is approved for the indication being sought in providing anesthesia for various ophthalmic procedures including refractive surgery, intravitreal injection and tonometry.

These trials are supported by an additional study which demonstrated that tetracaine 0.5% is as effective as lidocaine 2% in providing adequate anesthesia for clear corneal surgery.

1 Than TP, Bartlett JD. Chapter 6: Local Anesthesia. In: Bartlett JD, Januus S, eds. *Clinical Ocular Pharmacology*, 5th ed. St. Louis: Butterworth-Heinemann; 2008: 85–95.

Four trials were submitted to support the use of tetracaine in the pediatric population (see Section 10 of this CDTL review). Each evaluated the use of tetracaine in strabismus surgery. Two of the studies were with tetracaine 0.5% and two used tetracaine 1%. While the studies conducted with the 0.5% formulation did not demonstrate efficacy; this was likely due to the design of the trials and not to the inability to anesthetize the pediatric eye. The support for the use of 0.5% in the pediatric population can be extrapolated from the adult population. This is appropriate since the effect of topical anesthesia on the ocular surface is similar in both populations.

# 8. Safety

From the Medical Officer Review dated 1/20/16:

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 which is rare since patients are normally not prescribed these drops for self-administration.

The safety data available for review does not allow for a quantitative determination of the exact incidence of each type of adverse events. Pooling of the safety results from the published reports and postmarketing data is not appropriate.

The studies described in Section 7 of this CDTL review and additional published works by Havener 1983, McGee 2007 and Bartlett 2007 were reviewed for safety information. Each cover the toxicities associated with topical ophthalmic anesthetics.

**Common Adverse Events**

The reporting of adverse events in the literature provided for review was sparse. The majority of the papers did not address adverse events. Chalam 2009 did report that there was a 3% rate of corneal edema that could have been due to the surgical intervention. Both Moshirfar 2014 and Shafi 1998 noted pain on instillation of the anesthetic drop. Barequet 1999 did not note any ocular surface toxicity during their study.

Since the adverse event reporting in the papers reviewed was lacking, two review articles on the toxicity of topical anesthetics Havener 1983 and McGee 2007 were provided. Each investigated the toxicities associated with topical ophthalmic anesthetics. While these do not give the exact rates of expected adverse events, they can provide an example of the types of events that may be associated with the use of topical tetracaine.

Havener 1983 reports:

- Most patients receiving topical administration of tetracaine eye drops report *burning sensation* of about 30 seconds in duration

- Patients will typically experience *numb sensation* in the instilled eye ranging in duration from 10 to 20 minutes depending on dosage (number of drops).
- Tetracaine anesthetic has the potential to cause superficial *corneal epithelial lesions*, which intensifies with repeated administration; therefore, it is recommended that tetracaine not be prescribed for patient home-use.
- In rare cases, tetracaine may cause *allergic contact dermatitis* after repeated use.
- Physicians are warned not to hyperdermically inject tetracaine solution for ophthalmologic procedures as cases of *death* have been reported.

McGee 2007 reports:

- Patients receiving topical ophthalmic anesthetics often experience *stinging* and *discomfort* in the affected eye.
- Topical anesthetics reportedly have the potential to cause *punctate corneal epithelial erosions* as well as inhibit the migration of corneal epithelial cells and to cause direct damage to their microvilli.
- Systemic side effects associated with topical ophthalmic anesthetics have also been reported, including *anxiety*, *shortness of breath*, and *seizure*.

**Product-Related Impurities and** (b) (4)

The drug product specifications include tests for (b) (4) that are controlled at NMT (b) (4)% and (b) (4)%. These limits are based on the batch release and stability data provided in the NDA. These impurities and the (b) (4) in the drug product specifications) have not been specifically tested in non-clinical studies.

Per the applicant's 2/17/2016 submission (SDN012):

> For 30+ years until 1999, Tetracaine HCl STERI-UNIT was manufactured in the (b) (4) with 2 mL fill in (b) (4) The significant manufacturing changes that have occurred for TETRACAINE HCL STERI-UNIT include the following:
>
> April 1996: Change in (b) (4) The change in (b) (4) was reviewed and approved by FDA for other blister packaged products (reference MIOSTAT NDA 16-968/S-014; approved Jun. 1996).
>
> December 1999: The most recent major change to the manufacturing process was transfer of commercial manufacturing to (b) (4) with switch to 4 mL target fill volume in 4 mL MDPE bottles using (b) (4)mm dispensing plugs and (b) (4)mm closures. The change was supported by stability batches manufactured in 1996 using the new container closure system and fill volume. (b) (4) manufacturing using the MDPE bottle was reviewed and approved by FDA for other products.

In an information request from the Agency dated 2/3/2016, the applicant was asked to provide information on the toxicity anticipated from the unqualified impurities (if any) and post-marketing adverse event reporting for your product in the last two decades. The Agency had previously requested historic results of impurity testing

Per the applicant's 2/17/2016 submission (SDN012), the past 5 years of analytical data were reviewed.

(b) (4)

Per the applicant's 2/17/2016 submission (SDN012), no toxicity is anticipated from the unqualified impurities for the intended use of the product.

A total of 86 post-market adverse events (70 cases) were reported for Tetracaine SteriUnits since 1997 (see table below), which translates to an overall reporting rate of <4.2 events per (b) (4) units sold. Sales data was available from 2000 to 2015. MedWatch forms for these cases were provided.

**Table 2 Post Market Adverse Events for Tetracaine SteriUnits 1997-2015**

| BODY_SYS | PREF_TERM | 1997 | 1999 | 2000 | 2001 | 2002 | 2004 | 2005 | 2006 | 2008 | 2009 | 2010 | 2011 | 2014 | 2015 | Grand Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cardiac disorders | Bradycardia | | | | | | | | | | | | | 1 | | 1 |
| Cardiac disorders Total | | | | | | | | | | | | | | 1 | | 1 |
| Eye disorders | Corneal opacity | 1 | | | | | | | | | | | | | | 1 |
| | Eye irritation | | | 1 | | | | | 1 | | | | | | | 2 |
| | Eye pain | | | 1 | | | | | | | | | | 1 | | 2 |
| | Eyelid ptosis | | | 1 | | | | | | | | | | | | 1 |
| | Mydriasis | | | | | | | | | | | | | 1 | | 1 |
| | Ocular discomfort | | 3 | 2 | 4 | | | | 2 | | | | | | | 11 |
| | Ocular hyperaemia | | | | | | | | 1 | | | | | | | 1 |
| | Vision blurred | | | | | | | | | | | | | 1 | 1 | 2 |
| | Vitreous floaters | | | | | | | | | | | | | | 1 | 1 |
| Eye disorders Total | | 1 | 3 | 5 | 4 | | | | 4 | | | | | 3 | 2 | 22 |
| General disorders and administra | Drug effect decreased | | | | | | 1 | | 1 | | | | | | | 2 |
| | Drug ineffective | | | 1 | 1 | 2 | | 1 | 2 | | | | | 2 | 1 | 10 |
| | No adverse event | | 1 | | | | | | | | | | | | | 1 |
| General disorders and administration site conditions Total | | | 1 | 1 | 1 | 2 | 1 | 1 | 3 | | | | | 2 | 1 | 13 |
| Immune system disorders | Hypersensitivity | | | | | | | | | 1 | | | | | 1 | 2 |
| Immune system disorders Total | | | | | | | | | | 1 | | | | | 1 | 2 |
| Infections and infestations | Endophthalmitis | | | | | | | | | | | | 3 | 7 | | 10 |
| Infections and infestations Total | | | | | | | | | | | | | 3 | 7 | | 10 |
| Injury, poisoning and procedural | Circumstance or information capable of leading to medication error | | | | | | | | | | 1 | 1 | | | | 2 |
| | Off label use | | | | | | | | | | | | | 4 | | 4 |
| | Toxic anterior segment syndrome | | | | | | | | | | | | 15 | 11 | 2 | 28 |
| Injury, poisoning and procedural complications Total | | | | | | | | | | | 1 | 1 | 15 | 15 | 2 | 34 |
| Investigations | Heart rate increased | | | | | | | | | | | | | | 1 | 1 |
| | Oxygen saturation decreased | | | | | | | | | | | | | 1 | | 1 |
| Investigations Total | | | | | | | | | | | | | | 1 | 1 | 2 |
| Nervous system disorders | Headache | | | | | | | | | | | | | | 1 | 1 |
| | VIIth nerve paralysis | | | 1 | | | | | | | | | | | | 1 |
| Nervous system disorders Total | | | | 1 | | | | | | | | | | | 1 | 2 |
| Grand Total | | 1 | 4 | 7 | 5 | 2 | 1 | 1 | 7 | 1 | 1 | 1 | 18 | 29 | 8 | 86 |

Serious post-market adverse events were:

- Toxic anterior segment syndrome (TASS) (n=28)
- Endophthalmitis (n=10)
  - 3 co-reported with TASS
- Oxygen saturation decreased (n=1); Bradycardia (n=1);
  - same case (neonate with medical history of low oxygen saturation and bradycardia
- Off label use (n=1)
  - co-reported with a TASS case.

All reports of TASS were associated with cataract surgery/IOL implantation. TASS is a known potential complication following cataract surgery. All reports of endophthalmitis were associated with cataract surgery/IOL implantation. Endophthalmitis is a known potential complication following cataract surgery.

## Safety Summary Statement

Multiple adequate and well controlled studies demonstrate the safety of tetracaine hydrochloride ophthalmic solution 0.5% in producing rapid and short-acting topical ophthalmic anesthesia.

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 which is rare since patients are normally not prescribed these drops for self-administration.

The applicant has satisfactorily demonstrated that there have been no manufacturing changes since 1999, and that the product-related impurities and (b) (4) were present in historical lots of the product. The post-market adverse event data submitted is consistent with the literature and supports the applicant's position that there is no toxicity is anticipated from the unqualified impurities for the intended use of the product.

## 9. Advisory Committee Meeting

No Advisory Committee was necessary or convened for this drug product.

## 10. Pediatrics

The applicant has submitted literature containing adequate and well controlled trials to assess the safety and efficacy of tetracaine in the pediatric population. See the following table. There is also literature describing safety of tetracaine in a prospective interventional non-comparative case series in premature infants (i.e. mean 33.5±2.4 weeks with range: 31–38.4 weeks) with high-risk prethreshold or threshold ROP.

Listing of Published Studies Submitted by the Applicant

| Study Design | Study Objectives | No. of Patients | Dosing Regimen | Reference |
|---|---|---|---|---|
| Randomized, observer masked | To assess the effect of topical tetracaine (amethocaine) on postoperative analgesia after strabismus surgery in children | 40 (1–12 yrs) | 2 drops of 1% tetracaine versus placebo (saline) | Watson 1991 |
| Randomized, controlled, observer masked | To test the effect of tetracaine on reducing postoperative pain, vomiting, and length of stay in children having strabismus repair | 62 (6 mos–15 yrs) | 2 drops of 0.5% tetracaine, subconjunctival bupivacaine 0.5%, or placebo (saline) | Carden 1998 |
| Randomized, double-masked, placebo-controlled | To compare the effect of placebo to intraoperative 0.5% topical tetracaine (amethocaine) or 0.5% topical ketorolac on pain control after strabismus surgery in children | 51 (2–7 yrs) | 2 drops of 0.5% tetracaine, 0.5% ketorolac, or placebo (saline) at the start and end of strabismus repair surgery | Kim 2003 |
| Randomize, 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 yrs) | 2 drops of 1% tetracaine before and after surgery with placebo (saline) controls | Anninger 2007 |

Additional Published Study

Castellanos MA1, Schwartz S, Leal R, Chan RV, Quiroz-Mercado H. Pain assessment in premature infants treated with intravitreal antiangiogenic therapy for retinopathy of prematurity under topical anesthesia. Graefes Arch Clin Exp Ophthalmol. 2013 Feb;251(2):491-4. doi: 10.1007/s00417-012-2060-2. Epub 2012 May 18

There is adequate information in the literature to support the safety of tetracaine hydrochloride ophthalmic solution in the pediatric population (all pediatric age groups). Efficacy of tetracaine hydrochloride ophthalmic solution for use in pediatric patients has been extrapolated from the adult population.

This application was presented, at the Pediatric Review Committee (PeRC) for a pediatric assessment on January 20, 2016. PeRC agreed with the Division's assessment that there is adequate information in the literature to support the safety of tetracaine hydrochloride ophthalmic solution in the pediatric population (all pediatric age groups).

# 11. Other Relevant Regulatory Issues

**OSI**
An Office of Scientific Investigations (OSI) audit was not requested. This is a 505(b)(2) application primarily based on literature.

**FINANCIAL DISCLOSURE**
This is a 505(b)(2) new drug application primarily based on literature. In accordance with 21 CFR Part 54, no financial disclosure is appropriate for this application. There are no "covered clinical studies" in this submission.

**DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA)**
In a review finalized 1/12/2016, DMEPA has reviewed the proposed carton labeling, bottle label and prescribing information. DMEPA provided recommendations on the packaging configuration and the package insert labeling. These are incorporated into the Medical Officer's labeling where appropriate, but the originally submitted carton and container packaging revised by DMEPA have required substantial revision.

**OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)**
In a review finalized 1/27/2016, OPDP has reviewed the proposed product labeling (i.e., package insert). The Division has retained the word "rapid" in Section 1 because this is supported by the submitted literature and is important information for the physician.

**BIOSTATISTICS**
Per the Biostatistics consultative review finalized 1/21/2016:

The efficacy summary for this review is based on nine publications. Eight of the nine publications were selected by the applicant and one publication was identified by this reviewer. All nine publications were randomized and controlled studies. In seven of these publications, only an active control was included and in the remaining two publications both an active control and a placebo (saline) were included. The lidocaine gel 2% was the active control in four of the nine publications while proparacaine 0.5% (NDA 40277) was used in two publications. Proxymetacaine, bupivacaine and ketorolac were the active controls used in the remaining three studies (Table 1).

**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 2009* | 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 |
| | | | | (b) (4) |
| 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 |
| | | | | (b) (4) |
| 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 |

Source: Applicant's summary and the *reviewer's summary based on submitted publications

The average pain score or the proportion of subjects who experienced little or no intraoperative and/or no postoperative pain, or the rate of successful tonometry were reported as efficacy endpoints in the nine published studies. Because the published studies used slightly different scales for pain measurement and evaluated different dosing regimen 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 a statistically significant efficacy results for tetracaine 0.5% (Table 2). The results in two of these publications (Rifkin 2009 and Moshirfar 2014) should be interpreted with caution because the results in Moshirfar 2014 were not adjusted for multiple comparisons, and the reviewer's analysis of the data from Rifkin 2009 did not show statistically significant results for the pairwise comparison of tetracaine 0.5% to the other treatment groups.

**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) |
| (b) (4) | | |
| Barequet 1999 | Cochet–Bonnet aesthesiometer<br>0 = no sensation<br>6 =maximum sensation<br>Pain scale:<br>0 = no pain<br>1 = minimal pain<br>2 = moderate pain<br>3=significant 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%)) |
| (b) (4) | | |
| 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 |

Source: Reviewer's summary based on submitted publications

# 12. Labeling

NDA 208135, Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT®, is recommended for approval for procedures requiring a rapid and short-acting topical ophthalmic anesthetic with the labeling found in the Appendix at the end of this CDTL review.

# 13. Recommendations/Risk Benefit Assessment

**RECOMMENDED REGULATORY ACTION:**
NDA 208135, Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT®, is recommended for approval for procedures requiring a rapid and short-acting topical ophthalmic anesthetic.

Topical administration of tetracaine hydrochloride ophthalmic solution 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.

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 which is rare since patients are normally not prescribed these drops for self-administration.

**RISK BENEFIT ASSESSMENT:**
In 2015, Alcon sold approximately (b) (4) units in the United States as a marketed, unapproved product. This number has gradually increased since 2001 when the number of units was (b) (4) (b) (4) (b) (4)

The applicant has satisfactorily demonstrated that there have been no manufacturing changes since 1999, and that the product-related impurities and (b) (4) were present in historical lots of the product. The post-market adverse event data submitted is consistent with the literature and supports the applicant's position that there is no toxicity is anticipated from the unqualified impurities for the intended use of the product.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

**RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:**
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.

# Appendix

The package insert and 12 x 4 mL carton labeling, submitted by the applicant on February 26, 2016, and the container, blister, and carton sticker label submitted by the applicant on February 24, 2016, are acceptable. As a minor editorial correction, "an ester local anesthetic" should be moved from the Full Prescribing Information Section 1 to the Highlights *Indications and Usage* section of the PI in the final printed labeling.

(b) (4)

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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WILLIAM M BOYD
02/29/2016

WILEY A CHAMBERS
02/29/2016