

CLINICAL REVIEW

Application Type	N
Application Number(s)	NDA 208-135 P-IND (b) (4)
Priority or Standard	Standard
Submit Date(s)	April 30, 2015
Received Date(s)	April 30, 2015
PDUFA Goal Date	February 29, 2016
Division / Office	DTOP/OAP
Reviewer Name(s)	Jennifer Harris, M.D.
Review Completion Date	October 15, 2015
Established Name	Tetracaine hydrochloride ophthalmic solution 0.5%
(Proposed) Trade Name	Tetracaine hydrochloride ophthalmic solution 0.5% Steri- Unit
Therapeutic Class	anesthetic
Applicant	Alcon Research, Ltd.
Formulation(s)	Ophthalmic solution
Dosing Regimen	One drop topically in the eye(s) as needed
Indication(s)	For procedures requiring a rapid and short-acting topical

Intended Population(s)	ophthalmic anesthetic Patients requiring a rapid and short-acting topical ophthalmic anesthetic.
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Tetracaine hydrochloride ophthalmic solution 0.5% is recommended to be approved for procedures requiring a rapid and short-acting topical ophthalmic anesthetic

1.2 Risk Benefit Assessment

The benefit risk profile of tetracaine 0.5% supports its use as a topical ophthalmic anesthetic. The submitted literature reports demonstrate the efficacy of the products for inducing anesthesia prior to various ophthalmic procedures. The reference data and post-marketing reporting confirm that tetracaine 0.5% is safe for use as a short-acting anesthetic. The adverse events associated with its use are non-serious and mostly related to the pain/discomfort felt on instillation of the drop.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no postmarket risk evaluation or mitigation strategies recommended for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no postmarket requirements or commitments recommended for this product.

2 Introduction and Regulatory Background

2.1 Product Information

Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT is a sterile, preservative free formulation of tetracaine, currently marketed as an unapproved drug in the U.S. by Alcon, Inc., and has been sold in the US for approximately 20 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.

2.2 Tables of Currently Available Treatments for Proposed Indications

Approved Drugs

Tradename	Established Name	NDA Number	Indication
Alcaine	Proparacaine 0.5%	ANDA 080027	Proparacaine Hydrochloride Ophthalmic Solution is 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%	NDA022221	local anesthetic indicated for ocular surface anesthesia during ophthalmologic procedures

2.3 Availability of Proposed Active Ingredient in the United States

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. The active ingredient has also been approved for marketing for two dermatologic products (NDA 21717 and NDA 21623)

2.4 Important Safety Issues with Consideration to Related Drugs

There are no specific safety concerns that have arisen specific to other available topical ophthalmic anesthetics. The safety profiles are similar.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Ophthalmic solutions of tetracaine have the status of “unapproved drug” by the U.S. Food and Drug Administration. Tetracaine’s ophthalmic use predates the Kefauver–Harris Amendments of 1962.

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

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The original submission from the Applicant did not allow for a substantive review of the product without requiring additional information. Additional clinical information was requested from the applicant and supplemental literature searches were conducted by the Agency.

3.2 Compliance with Good Clinical Practices

No clinical trials were conducted by the Applicant to assess the safety and/or efficacy of tetracaine hydrochloride as a topical anesthetic for ophthalmic procedures.

3.3 Financial Disclosures

No covered clinical studies are included in this application and, therefore, no financial certification or financial disclosure, as outlined in 21 CFR 54.4, was provided by the sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Tetracaine Hydrochloride is a compendial drug substance. Tetracaine Hydrochloride Ophthalmic Solution, 0.5% is supplied in a medium density natural polyethylene (MDPE) round bottle with a natural low density polyethylene (LDPE) flat tip dispensing plug and polypropylene (PP) closure. The product has a 4 mL fill in 4 mL configuration and blister packed. Formulation composition and primary packaging are the same as the marketed product.

Composition of Tetracaine Hydrochloride Ophthalmic Solution, 0.5%

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)	(b) (4)	USP
Acetic Acid and/or (b) (4)	Target pH 4.5	pH Adjustor	NF USP
Water for Injection	(b) (4)	(b) (4)	USP

^a (b) (4)

4.2 Clinical Microbiology

N/A - Not applicable for this application.

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical testing was conducted with tetracaine hydrochloride to support the current application. Only limited information on the pharmacology and pharmacokinetics of the compound is available through literature reports provided by the applicant. See the pharmacology/toxicology review for a thorough review of these references.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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.

4.4.2 Pharmacodynamics

Pharmacodynamic studies have not been conducted for this product by the applicant; however, prior studies have studied the duration of anesthesia for tetracaine. Bartfield 1994 found a duration of action for tetracaine to last approximately 9.4 minutes. Nomura 2001 measured the duration of action of tetracaine by esthesiometry and found a duration of 10 minutes.

4.4.3 Pharmacokinetics

Pharmacokinetic studies have not been conducted for the product by the applicant.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

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 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 1 drop of 1% amethocaine* 5 min apart × 3 in fellow eye	No (1% solution)
(b) (4)					
Tsoumani 2010	Randomized, controlled, double-	To compare the efficacy of tetracaine and the combination of	51	0.5 cm lidocaine 2% gel plus 1 drop of 0.5% tetracaine or 1 drop of 0.5% tetracaine 5 min	unknown

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	masked	lidocaine application and instillation of tetracaine as methods of topical anesthesia for cataract surgery		apart × 3	
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 yrs)	2 drops of 1% amethocaine* versus placebo (saline)	No (1% solution)
Carden 1998	Randomize, 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 mos–15 yrs)	2 drops of 0.5% amethocaine*, subconjunctival bupivacaine 0.5%, or placebo (saline)	Unknown
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 yrs)	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 yrs)	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% 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% TetraVisc Tetracaine 0.5%	TetraVisc (Cynacon/Ocusoft) 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% 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 Lidocaine 5%	Unknown
Sabermoghadam 2012	pilot study	to find a new form of lidocaine to give a sufficient level of anesthesia	30	Tetracaine Lidocaine cyclodextrin	unknown
Additional published article provided by the Agency					
Chalam 2009	randomized, multi-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)

(b) (4)

* Tetracaine is also known as amethocaine and pontocaine.

5.2 Review Strategy

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.

5.3 Discussion of Individual Studies/Clinical Trials

See section 6.1.4

6 Review of Efficacy

Efficacy Summary

The primary support for efficacy for tetracaine HCl 0.5% ophthalmic solution comes from 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. (See section 6.1.1 page 19 for further explanation)

Four trials were submitted to support the use of tetracaine in the pediatric population. 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.

6.1 Indication

The indication is for the use of tetracaine 0.5% for procedures requiring a rapid and short-acting topical ophthalmic anesthetic.

6.1.1 Methods

The support for efficacy for tetracaine HCl 0.5% ophthalmic solution comes from Rifkin 2012, Chalam 2009, Moshifar 2014, Shafi 1998 (b) (4) **the recommendation for approval is only based on Moshifar 2014, Rifkin 2012 and Shafe 1998. Chalam 2009** (b) (4)

6.1.2 Demographics

	Rifkin 2012	*Chalam 2009	Moshifar 2014	Shafi 1998	(b) (4)
Number of Subjects	60	122	128	53	
Gender					
male	26	53	57	17	
female	34	69	71	36	

					(b) (4)
Age	>65 (n=35) <65 (n=25)	Mean=70.5	All>21 Mean=32.8	Mean=64.7 (19-87 years)	

***Not used as basis for approval recommendation.**

6.1.3 Subject Disposition

The effect of tetracaine was measure within minutes of the planned procedure/surgical intervention; therefore, all randomized subjects in the studies were available for evaluation.

6.1.4 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.

Reviewers Comments:

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

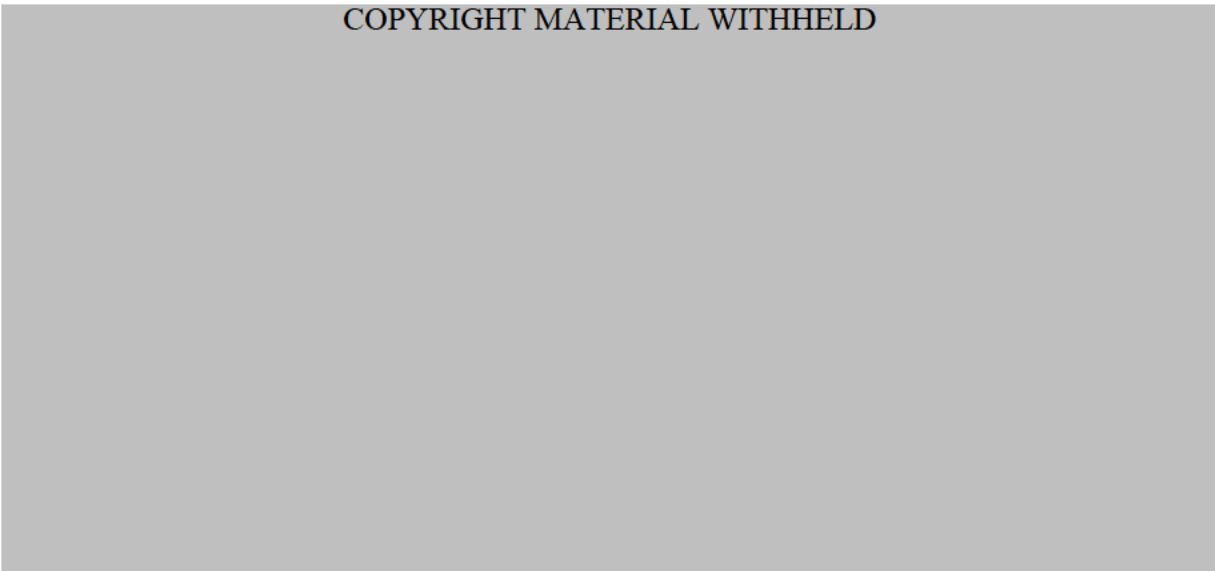
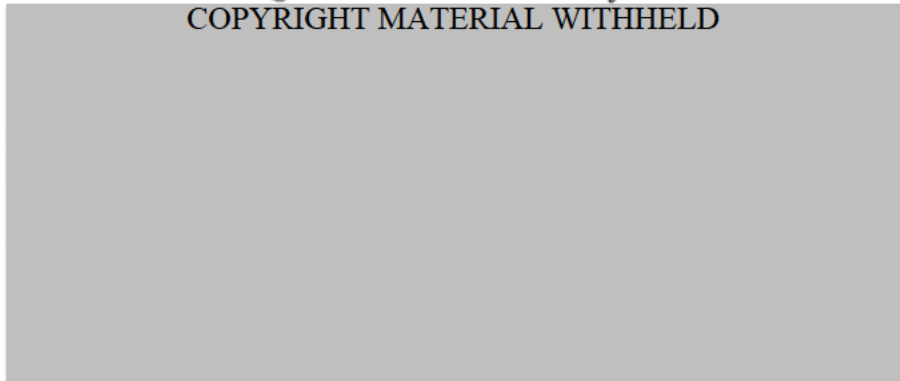


Fig. 2. Comparison of average pain scores of patients by demographics. Statistical significance was found with sex of the patient, age, perception of improvement of vision from previous injection and time of day of injection.

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





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 I Patient demographics and treatment data

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

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Reviewers Comments:

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)



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.

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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

Reviewers Comments:

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.

(b) (4) Barequet
1999 was used to support approval. (b) (4)

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

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)

Reviewer's comments: *Tetracaine and Lidocaine were effective in providing corneal anesthesia for clear corneal surgery.*



6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant currently markets tetracaine 0.5% which is dosed one drop as needed to induce anesthesia. Clinically, additional doses are sometimes given if adequate anesthesia has not been induced. The Applicant has not submitted data to change the currently labeled dosing recommendation.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy and/or tolerance effects studies with tetracaine have not been conducted by the Applicant, and no relevant reports of such studies have been identified in the published scientific literature.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable.

7 Review of Safety

Safety Summary

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. There are also rare reports of allergic reactions that usually occur after repeated administration over months to years.

7.1 Methods

No clinical trials were conducted by the Applicant to assess the safety of tetracaine hydrochloride (tetracaine) as a topical anesthetic for ophthalmic procedures; therefore, the safety of the product is based on published studies as well as postmarketing reports.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See section 5.3. In addition, additional published works by Havener 1983, McGee 2007 and Bartlett 2007 were reviewed. Each cover the toxicities associated with topical ophthalmic anesthetics.

7.1.2 Categorization of Adverse Events

The adverse event profile for tetracaine is based on the published studies and postmarketing reporting; therefore, the coding use to categorize adverse events is not available.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

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.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Due to the long history and frequent use of tetracaine ophthalmic solution, there has been adequate exposure for safety evaluation.

7.2.2 Explorations for Dose Response

The marketed dose for tetracaine ophthalmic solution is 0.5%. The recommended dosing is one drop to the eye; however, additional drops are sometimes given if adequate anesthesia has not been induced. Tetracaine 1% is also available (unapproved); however, it is not the standard of care for topical anesthesia due to reports of ocular irritation at the higher dose.

7.2.3 Special Animal and/or In Vitro Testing

Special animal/in-vitro testing has not been conducted for this product.

7.2.4 Routine Clinical Testing

N/A – routine clinical testing has not been conducted for topical ophthalmic tetracaine.

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A – metabolic, clearance and interactions was not conducted by the Applicant.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A - The safety profiles for topical ophthalmic anesthetics are similar.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in the literature reports submitted for review.

7.3.2 Nonfatal Serious Adverse Events

There were no serious adverse events reported in the literature reports submitted for review.

7.3.3 Dropouts and/or Discontinuations

The effect of tetracaine was measure within minutes of completing the planned procedure/surgical intervention; therefore, all randomized subjects in the studies were available for evaluation.

7.3.4 Significant Adverse Events

There were no severe adverse events reported in the literature reports submitted for review.

7.3.5 Submission Specific Primary Safety Concerns

N/A-there are no submission specific safety concerns.

7.4 Supportive Safety Results

7.4.1 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 hyperdermally 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*.

7.4.2 Laboratory Findings

No information on changes in patterns of laboratory tests associated with the use of topical ophthalmic tetracaine is available.

7.4.3 Vital Signs

No information on vital signs, physical findings, and other observations related to the safety of topical ophthalmic tetracaine is available.

7.4.4 Electrocardiograms (ECGs)

No information on vital signs, physical findings, and other observations related to the safety of tetracaine is available.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/clinical trials were conducted by the Applicant.

7.4.6 Immunogenicity

Allergic reactions to topical ocular tetracaine is believed to be extremely rare and develops in some patients after many months or years after repeated use (e.g. tonometry), Bartlett 2007. The usual clinical presentation is transient conjunctival hyperemia, chemosis, lacrimation and itching.

7.5 Other Safety Explorations

No studies or information on safety-related intrinsic or extrinsic factors, drug interactions, use during pregnancy or breast-feeding, overdose, dependence potential, rebound effects, and ability effects of tetracaine is available.

7.5.1 Dose Dependency for Adverse Events

N/A – see section 7.5

7.5.2 Time Dependency for Adverse Events

N/A – see section 7.5

7.5.3 Drug-Demographic Interactions

N/A – see section 7.5

7.5.4 Drug-Disease Interactions

N/A – see section 7.5

7.5.5 Drug-Drug Interactions

N/A – see section 7.5

7.6 Additional Safety Evaluations

No studies on safety-related intrinsic or extrinsic factors, drug interactions, use during pregnancy or breast-feeding, overdose, dependence potential, rebound effects, and ability effects of tetracaine were conducted by the Applicant.

7.6.1 Human Carcinogenicity

N/A – see section 7.6

7.6.2 Human Reproduction and Pregnancy Data

N/A – see section 7.6

7.6.3 Pediatrics and Assessment of Effects on Growth

Height and/or weight data is not available for the pediatric patients in the literature submitted for review. Studies have not been conducted to assess the effect of tetracaine on pediatric development.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Patients are not prescribed topical anesthetics due to the toxicities that can occur with repeated instillation. Rosenwasser 1990 reported cases of corneal ulceration, thinning and perforation, some requiring full thickness corneal transplantation with long term abuse.

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

Compiled postmarketing adverse event cases reported for Tetracaine Hydrochloride Ophthalmic Solution, 0.5% STERI-UNIT(Alcon Research, Ltd.) collected through pharmacovigilance through 31 December 2014

Clinical Review
 {Jennifer Harris, M.D.}
 {NDA 208135}
 {Tetracaine Hydrochloride Ophthalmic Solution 0.5% Steri-unit}

Body System	Preferred Term	Event Seriousness	Event Count
Cardiac disorders	Bradycardia	Serious	1
Cardiac disorders - Total			1
Eye disorders	Corneal oedema	Not serious	1
	Corneal opacity	Not serious	2
	Corneal thinning	Serious	1
	Eye irritation	Not serious	12
	Eye oedema	Not serious	3
	Eye pain	Not serious	9
	Eyelid ptosis	Not serious	1
	Foreign body sensation in eyes	Not serious	1
	Lacrimation increased	Not serious	1
	Mydriasis	Not serious	1
	Ocular discomfort	Not serious	19
	Ocular hyperaemia	Not serious	2
	Ulcerative keratitis	Not serious	1
Vision blurred	Not serious	3	
Visual acuity reduced	Not serious	1	
Eye disorders - Total			58
General disorders and administration site conditions	Drug effect decreased	Not serious	4
	Drug ineffective	Not serious	18
	No adverse event	Not serious	2
General disorders and administration site conditions - Total			24
Immune system disorders	Hypersensitivity	Not serious	1
Immune system disorders - Total			1
Infections and infestations	Endophthalmitis	Serious	9
Infections and infestations - Total			9
Injury, poisoning and procedural complications	Circumstance or information capable of leading to medication error	Not serious	2
	Corneal abrasion	Not serious	1
	Graft complication	Serious	1
	Medication error	Not serious	3
	Surgical procedure repeated	Serious	1
Toxic anterior segment syndrome	Serious	30	
Injury, poisoning and procedural complications - Total			38
Investigations	Oxygen saturation decreased	Serious	1
Investigations - Total			1
Nervous system disorders	Dizziness	Not serious	1
	Paraesthesia	Not serious	1
	VIIth nerve paralysis	Not serious	1

Clinical Review
 {Jennifer Harris, M.D.}
 {NDA 208135}
 {Tetracaine Hydrochloride Ophthalmic Solution 0.5% Steri-unit}

Body System	Preferred Term	Event Seriousness	Event Count
Nervous system disorders - Total			3
Respiratory, thoracic and mediastinal disorders	Throat tightness	Not serious	1
	Wheezing	Not serious	1
Respiratory, thoracic and mediastinal disorders - Total			2
Surgical and medical procedures	Off label use	Not serious	3
		Serious	3
Surgical and medical procedures - Total			6
Overall - Total			143
EVENT SERIOUS OVERALL COUNT			
Event seriousness		Seriousness Event Count	
Serious		47	
Not serious		96	
Overall - Total		143	

Ref. 2.7.4 Summary of Clinical Safety, Table 2.7.4.7-1

Reviewers Comment: *It should be noted that tetracaine is usually used as a part of a procedure along with other drug products. Many of the events reported are confounded by these factors.*

9 Appendices

9.1 Literature Review/References

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(b) (4)

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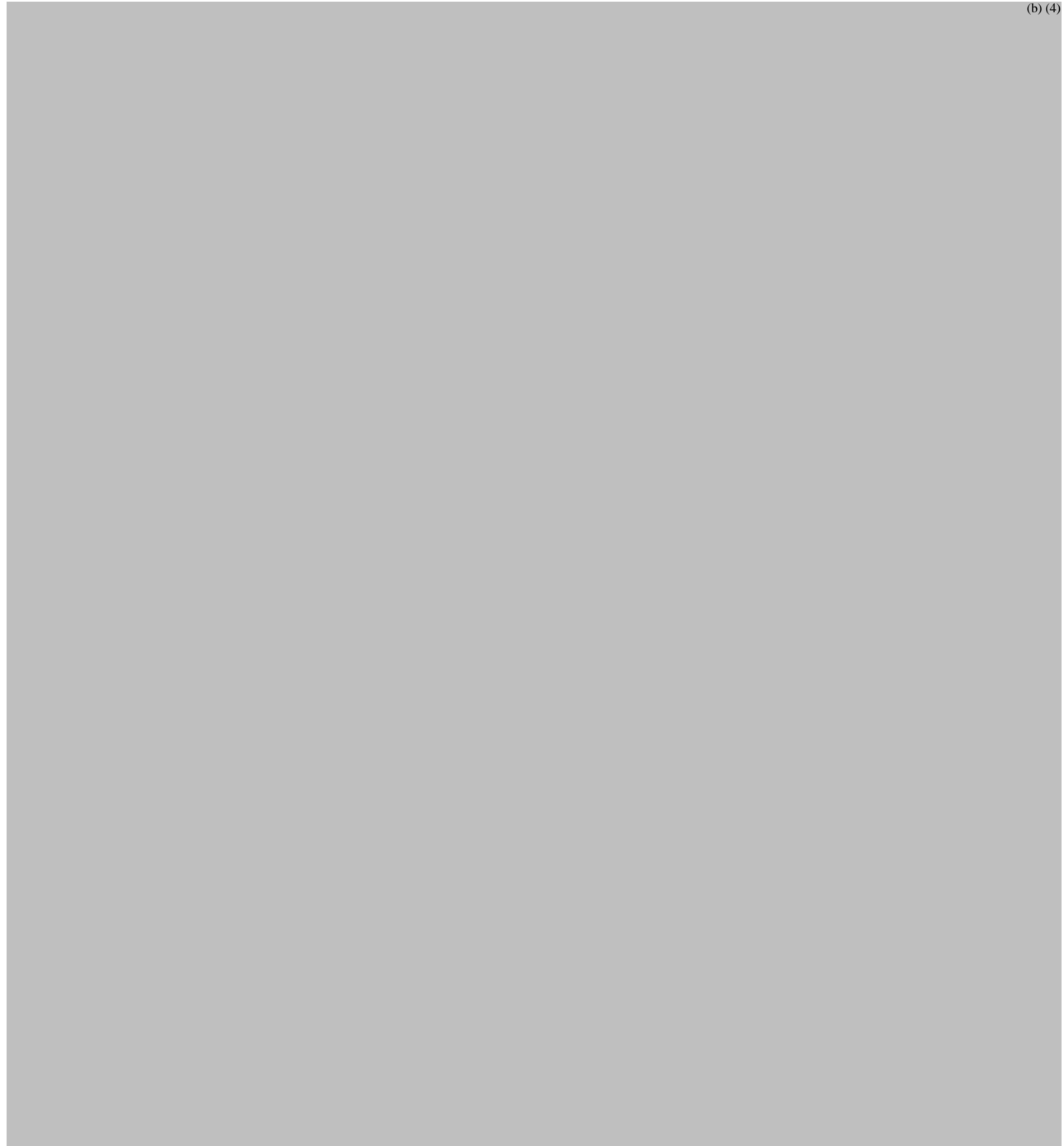
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9.2 Labeling Recommendations

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



9.3 Advisory Committee Meeting

N/A

9.4 Articles Not Used In Review

These 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.

Yu 2003

This study compared the efficacy of lidocaine 2% gel with amethocaine 1% eyedrops as the sole anesthetic agent for one-stage adjustable suture strabismus surgery. Fourteen (14) patients scheduled for bilateral and symmetrical strabismus surgery were enrolled. Each patient was randomized to receive lidocaine 2% in one eye and amethocaine 1% in the other. Subjective pain and discomfort perceived during surgery were obtained from the patient.

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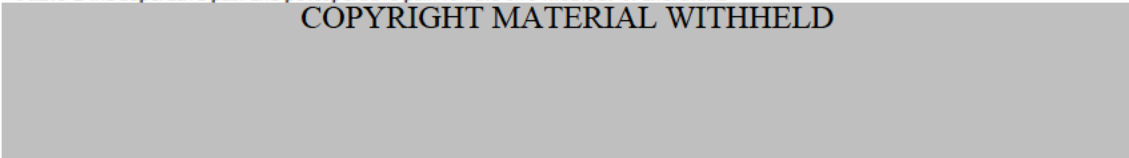
Figure 1. Patient subjective scores.

Tsoumani 2010

This study evaluated the level of pain during phacoemulsification in patients receiving either tetracaine 0.5% versus a combination of lidocaine 2% and tetracaine 0.5%. This was a prospective, randomized controlled study of 51 patients randomized between the two groups. One hour postoperatively, they were asked to grade their intraoperative and postoperative pain on a visual analog scale from 0 to 10.

Table 2 Intraoperative pain and postoperative pain for the two methods of anesthesia

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Watson 1991

This was a randomized study conducted to assess the effect of topical amethocaine 1% on postoperative analgesia requirements after strabismus surgery. Forty (40) children (age 1-12, mean 4) scheduled for elective surgery were randomized to either topical amethocaine or normal saline. Postoperative analgesia was evaluated with the use of a four-point assessment score over seven (7) timepoints.

	Mean Pain Score (range)
Amethocaine 1% (n=20)	11.4 (8-19)
Normal Saline (n=20)	19.5 (8-32)
p-value	P< 0.001

Reviewer’s Comments:

Twenty-five percent (25%) of subjects in the amethocaine groups required additional systemic pain meds post-op compared to 85% of subjects in the control group.

Carden 1998

This study was designed to test the hypothesis that adjunctive local anesthesia decreases post-operative pain, vomiting or length of stay in children having strabismus repair. This was a prospective, randomized, three-armed trial comparing topical amethocaine 1%, sub-conjunctival bupivacaine and topical normal saline. All treatments were given at the end of surgery but before emergence from anesthesia.

Reviewer’s comments:

The actual data is not provided in the paper for analysis. Only vertical bar graphs are included. The author’s conclusion is that “neither topical amethocaine nor sub-conjunctival bupivacaine makes a clinically significant difference in postoperative pain, emesis or length of stay”.

Kim 2003

This was a prospective randomized double blind placebo controlled study comparing the effect of placebo to intraoperative topical amethocaine 0.5% or ketorolac 0.5% on pain control after strabismus surgery in children. Fifty-one (51) children ages 2-7 were randomized to receive either normal saline, amethocaine 0.5% or ketorolac 0.5% at the start and end of surgery. Pain was assessed with a modified Children’s Hospital of Eastern Ontario Pain Score (CHEOPS) scale in the recovery room.

	Mean Pain Score
Amethocaine 0.5% (N=19)	5 (4-8)
Ketorolac (N=14)	5 (4-8)
Normal Saline (N=18)	5 (4-9)

Anninger 2007

This double-masked, randomized, controlled study enrolled eighty-eight (88) subjects aged 1 to 12 scheduled for strabismus surgery. Patients were randomized to one of three groups: group A received normal saline before and after surgery; group B received normal saline before and tetracaine 1% after surgery; group C received tetracaine 1% before and after surgery. A masked observer used a behavior scale and a modified behavior pain scale (MBPS) to assess pain in the post-anesthesia care unit.

Table 4. Postoperative emergence behavior scores: % of patients with scores of 1 or 2 (calm/asleep or slight agitation/fussy)

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Table 5. Postoperative pain scores: % of patients with MBPS score <5

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Sanabria 2013

This was a prospective, randomized, double-masked study designed to evaluate the efficacy of different anesthetics and topical anti-inflammatory treatment in patients undergoing intravitreal injection (IVI). Patients were randomized to two different preoperative anesthetic regimes (regime A [0.5% tetracaine+naphazoline] versus regime B [5% lidocaine]) and two different post-injection topical protocols (protocol 1 [tobramycin qid] versus protocol 2 [tobramycin qid+diclofenac qid]). Patients reported their pain using a numerical rating pain scale from 0 (no pain) to 10 (excruciating pain) immediately after the injection, 30 min and 24 h later.

	Mean Pain Score		
	Immediately	30 min	24 hr
Tetracaine+naphazoline (n=86)	2.85	2.00	1.81
Lidocaine (n=70)	2.67	1.58	1.77
p-value	0.727	0.210	0.979

Sabermoghadam 2012

This was a pilot study in 30 patients to find a new form of lidocaine to give a sufficient level of anesthesia. Lidocaine Cyclodextrin complex ophthalmic drop was produced and its pharmacological properties were studied. Patients were given tetracaine drop as the anesthetic: 3 drops separated 2 minutes apart, 10 min before the intervention. If a sufficient level of anesthesia was achieved, the procedure was done after. If the patient could not tolerate the procedure, the method was changed to lidocaine drop (administered after wash-out period like the first drop). The last option was conventional injection method if the patient could not tolerate the procedure with the second method either. Procedures such as forced duction test, symblepharon, pterygium, and Dysport injection into extra-ocular muscles were conducted. Patients used a 0 to 10 visual analogue scale for pain and a 0-4 scale for patient and physician satisfaction.

	Mean Pain Score
tetracaine	7.53±0.9
Lidocaine cyclodextrin	3.03±1.83
P value	0.00

Reviewer's Comments:

The concentrations of the drug products used in the trial were not provided. P-values were only reported out to 2 decimal points.

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/s/

JENNIFER D HARRIS
01/19/2016

WILLIAM M BOYD
01/20/2016