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RESEARCH**

APPLICATION NUMBER:

208135Orig1s000

MEDICAL REVIEW(S)

Deputy Division Director Review for NDA 208135

Date	February 21, 2016
From	Wiley A. Chambers M.D.
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A non-ophthalmic topical anesthetic spray of tetracaine was submitted in 1963, approved in 1965, and withdrawn in 1985 (NDA 14-766).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. This is a 505(b)(2) application referencing published literature.

2. Background

Listed below are approved drug products for similar indications. The outside of the immediate container of the majority of these products is not sterile. This application is for a topical ophthalmic anesthetic with the outside of the immediate container sterile being sterile.

Tradename	Established Name	NDA Number	Indication
Multiple	Proparacaine 0.5%	ANDA 80027 ANDA 40277 ANDA 87681 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

3. CMC

DRUG SUBSTANCE:

Nomenclature

USAN/INN name:

Tetracaine Hydrochloride

Chemical names:

Benzoic acid, 4-(butylamino)-, 2-(dimethylamino)ethyl ester, monohydrochloride (IUPAC)

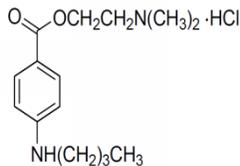
2-(Dimethylamino)ethyl *p*-(butylamino)benzoate monohydrochloride (IUPAC)

Benzoic acid, 4-(butylamino)-, 2-(dimethylamino)ethyl ester, monohydrochloride (CAS)

Other non-proprietary names:

CAS Registry No.: 136-47-0

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, 1H 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 (b)(4)%
Chromatographic purity	USP monograph	Individual Impurity: NMT (b)(4)% Total Impurities: NMT (b)(4)%
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)% Impurity (b)(4) NMT (b)(4)% Impurity (b)(4) NMT (b)(4)% Any Single Impurity: NMT (b)(4)% Total Impurities: NMT (b)(4)%

COMPOSITION OF THE DRUG PRODUCT:

Component	Amount (% w/v)	Function
Tetracaine Hydrochloride	0.5* (b)(4)	Active
Sodium Acetate (trihydrate)	(b)(4)	(b)(4)
Sodium chloride	(b)(4)	(b)(4)
Acetic acid (b)(4)	Target pH of 4.5	pH Adjustor
Water for Injection	(b)(4)	(b)(4)

* (b)(4)

Impurities Degradation Products

The potential degradation products of tetracaine hydrochloride in the finished drug product are shown below:

Degradation Product	Structure	RRT
(b) (4)		

⁴ Specified Impurities

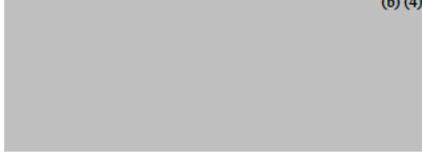
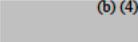
All of the potential degradation products are controlled in the finished drug product by a specific, stability-indicating, HPLC method. Impurity (b) (4) are specified degradation products. (b) (4) are oxidation degradation products created by the (b) (4) and (b) (4) are the only degradation products observed at levels \geq (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. As noted by the use of an (b) (4) the impurity profile appears to have been essentially unchanged over the past 30 years.

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.

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  Any Single Unspecified Impurity ^c Total Impurities	NMT ^{(b) (4)} % of Active ^{(b) (4)} % of Active NMT ^{(b) (4)} % of Active
pH (Potentiometric)	
Osmolality (Freezing Point Depression)	^{(b) (4)} mOsm/kg
Appearance (Visual): Color Clarity Precipitate	 NMT Ph. Eur. II None
Particulate Matter by HIAC	Meets USP Requirements NMT ^{(b) (4)} particles/m  NMT ^{(b) (4)} particles/mL  NMT ^{(b) (4)} particles/mL 
Sterility, Contents ^d	Meets USP Requirements
Sterility, Exteriors ^d	Meets USP Requirements

^a Release Test only

^b Report any impurity \geq ^{(b) (4)} % of active

^c  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

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.

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)	(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 0 (b) (4) for profile code CSN with a status of NAI. 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)	(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. Recommendation: Waive Inspection - Acceptable based on history/profile and DO Recommendation	Acceptable as of 12/11/2015
(b) (4)	(b) (4)	(b) (4) Finished drug product (b) (4) sterilizer	Process related impurities/ degradants (b) (4); adequate validation and monitoring (control on exposure of drug product to the (b) (4) needed for product quality	Last inspection Assign inspection 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.

5. Clinical Pharmacology/Biopharmaceutics

The applicant did not conduct any clinical pharmacology related studies and requested the waiver of evidence of in vivo bioavailability or bioequivalence. In accordance with the 21 CFR §320.22(e), the 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

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.

7. Clinical/Statistical - Efficacy

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.

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)					
Tsouman i 2010	Randomized, controlled, double- masked	To compare the efficacy of tetracaine and the combination of lidocaine application and instillation of tetracaine as methods of topical anesthesia for cataract surgery	51	0.5 cm lidocaine 2% gel plus 1 drop of 0.5% tetracaine or 1 drop of 0.5% tetracaine 5 min apart × 3	unknown
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, 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 years)	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 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% 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 (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
Sabermoghdam 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.

Details of these clinical trials are covered in the Clinical and Statistical Reviews. The simple fact that cataract surgery was able to be performed with tetracaine as the only anesthetic demonstrates the efficacy of tetracaine in producing an anesthetic effect. As described in the regulations for adequate and well controlled studies, 21 CFR 314.126, patients could have been their own control (i.e., historical control) because anesthesia would not otherwise be expected to occur. The studies are not sufficiently powered to be able to establish whether tetracaine, proparacaine or lidocaine is more effective than any of the other topical ophthalmic anesthetics.

8. Safety

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

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. 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 million units sold.

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	6	4				4					3	2	22
General disorders and administration site conditions	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
Immune system disorders Total										1						1
Infections and infestations	Endophthalmitis												3	7		10
Infections and infestations Total													3	7		10
Injury, poisoning and procedural complications	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
	Vllth 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 included: toxic anterior segment syndrome (TASS) (n=28), endophthalmitis (n=10), oxygen saturation decreased (n=1); Bradycardia (n=1). These events have all been associated with cataract surgery and are unlikely to be related to the use of the anesthetic.

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.

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.

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

Castellanos MA, 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.

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 at the end of this 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:

The applicant has satisfactorily demonstrated that there have been millions of uses and no manufacturing changes since 1999, and that the product-related impurities and sterilization process residues 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 minimal 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.

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/s/

WILEY A CHAMBERS
02/26/2016

CLINICAL REVIEW

Application Type	N
Application Number(s)	NDA 208-135 P-IND 115,866
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

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

	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.

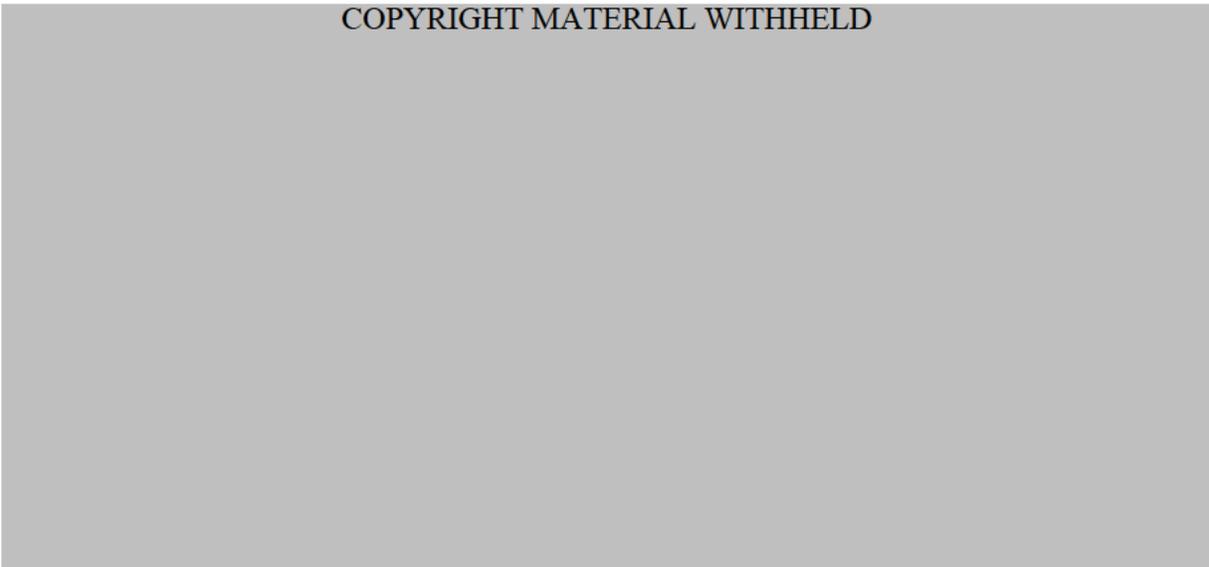
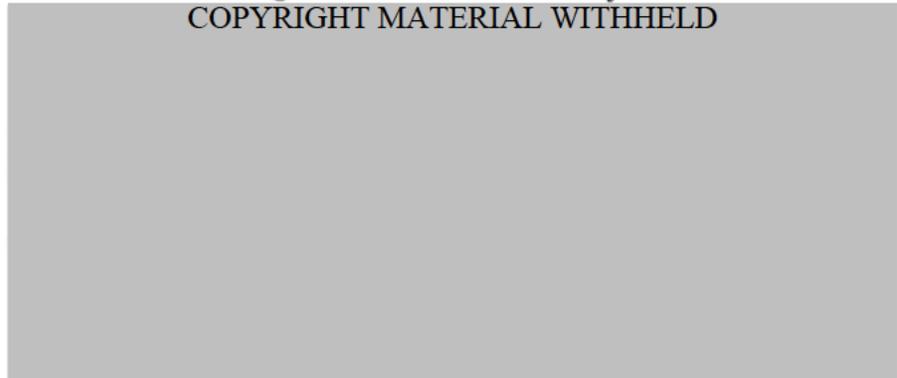


Fig. 2. Comparison of average pain scores of patients by demographics. Statistical significance was found with sex of the patient, age, perception of improvement of vision from previous injection and time of day of injection.

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.



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.

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Reviewers Comments:

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

Moshirfar 2014

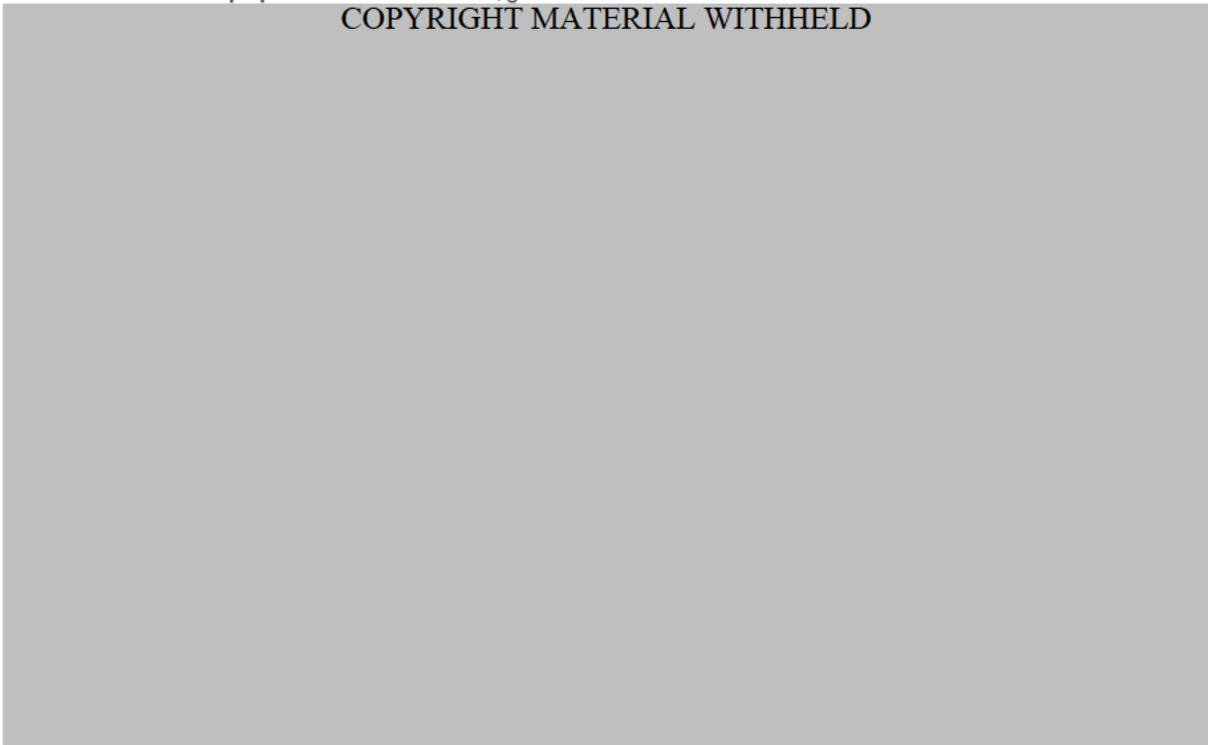
This was a prospective, single-masked, randomized study of 256 eyes from 128 patients being treated with Lasik or PRK who received either tetracaine 0.5% in one eye and proparacaine in the other. Pain levels were graded on a 0-10 scale and were assessed upon instillation, during surgery, immediately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

Table 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.

1999 was used to support approval. ^{(b) (4)} Barequet ^{(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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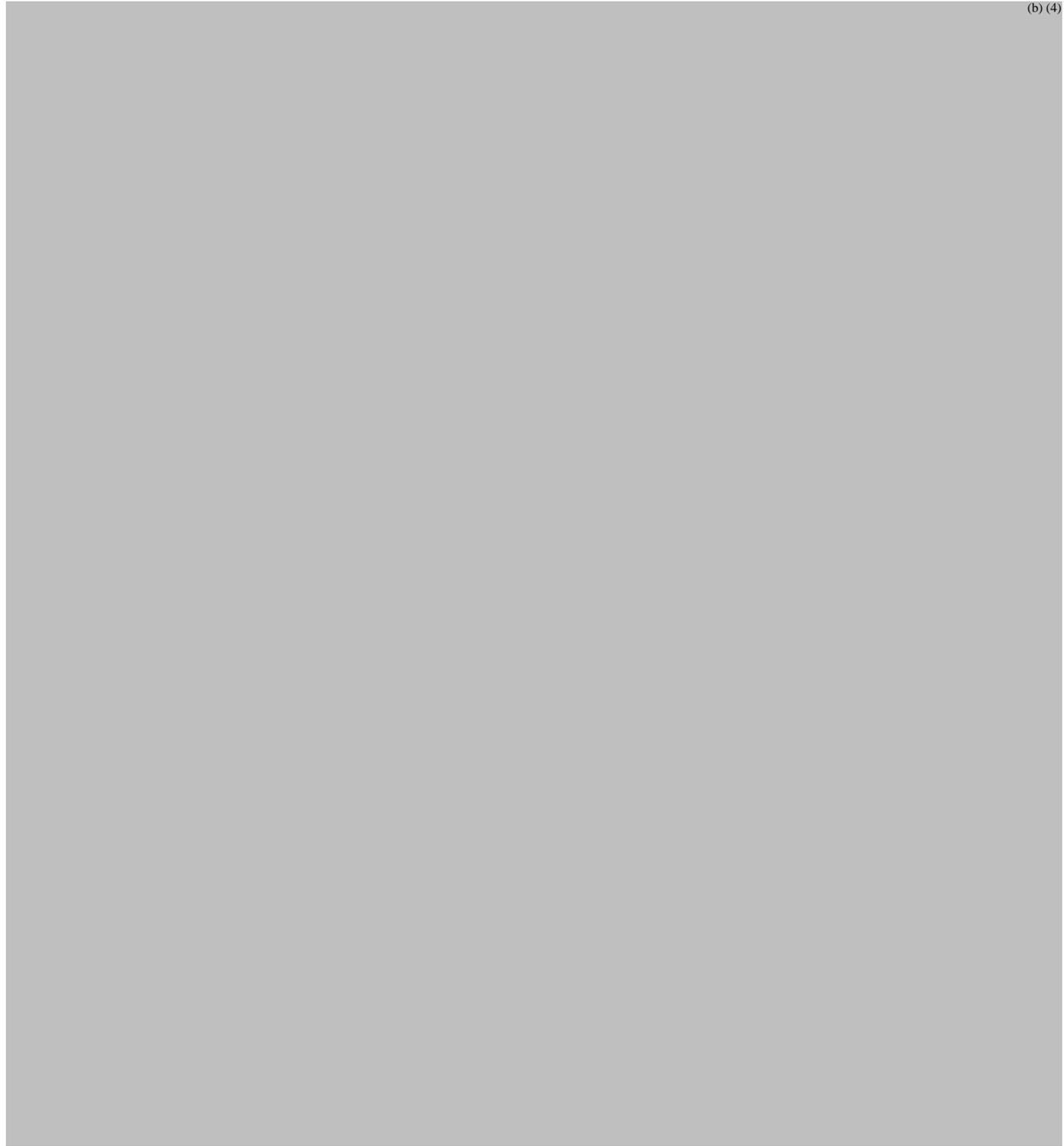
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9.2 Labeling Recommendations

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.



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

	Anesthesia	n	Mean	Standard deviation	Standard error mean
Intraoperative pain	Tetracaine eyedrops	27	4.19	2.321	0.447
	Tetracaine drops + lidocaine gel	24	3.88	2.724	0.556
Postoperative pain	Tetracaine eyedrops	27	1.11	1.625	0.313
	Tetracaine drops + lidocaine gel	24	1.58	1.666	0.340

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208135 Applicant: Alcon Research Stamp Date: April 30, 2015

Drug Name: Tetracaine NDA/BLA Type:505(b)(2)
Hydrochloride Ophthalmic
Solution 0.5% Steri-Unit

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	√			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	√			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	√			
5.	Are all documents submitted in English or are English translations provided when necessary?	√			
6.	Is the clinical section legible so that substantive review can begin?	√			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	√			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	√			
9.	Has the applicant submitted the integrated summary of safety (ISS)?		√		
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		√		
11.	Has the applicant submitted a benefit-risk analysis for the product?	√			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505(b)(2)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				Tetracaine hydrochloride ophthalmic solution 0.5%
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			√	The applicant currently markets the reference drug as an "unapproved drug"
15.	Describe the scientific bridge (e.g., BA/BE studies)			√	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title:		√		

File name: 5_Clinical Filing Checklist for NDA 208135

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: _____ Arms: _____ Location in submission: _____				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? <div style="background-color: #cccccc; padding: 5px; text-align: right;">(b) (4)</div> Pivotal Study #4 – Tsoumani 2010 – Tetracaine 0.5% eyedrops with or without lidocaine 2% gel in topical anesthesia for cataract surgery	√			The applicant has provided a total of nine (9) articles from the literature to support the requested indication.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	√			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	√			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		√		
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?		√		The applicant has submitted two (2) review articles and postmarketing safety data to support the safety of this product.
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?		√		
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	√			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	√			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	√			
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		√		
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?		√		
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		√		
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			√	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			√	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	√			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			√	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		√		
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		√		
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?			√	Format not discussed with Division
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		√		
37.	Are all datasets to support the critical safety analyses available and complete?		√		
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?		√		
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?		√		
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?		√		

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA 208135

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Jennifer D. Harris, M.D.

 Reviewing Medical Officer

06/03/2015

 Date

 Clinical Team Leader

 Date

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

/s/

JENNIFER D HARRIS
07/06/2015

WILLIAM M BOYD
07/07/2015