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 (b) (4) A non-ophthalmic topical anesthetic spray of tetracaine was submitted in 1963, approved in 1965, and withdrawn in 1985 (NDA 14-766).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

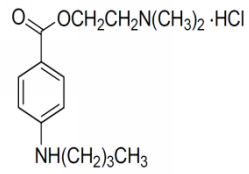
3. CMC

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, ^{1}H and ^{13}C NMR and mass spectra are consistent with the proposed structure.

Tests and Specifications for Tetracaine Hydrochloride Drug Substance

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

[a] 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) Impurity B and (b) (4) are the only degradation products observed at levels ≥ (b) (4) % in product stability studies up to 24 months. The other specified degradation products were seen at relatively low levels in product stability studies up to 24 months. 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)	(b) (4)% label
Tetracaine Hydrochloride Identity (HPLC)[b] (b) (4) Any Single Unspecified Impurity[c] Total Impurities	 NMT (b) (4)% of Active (b) (4)% of Active NMT (b) (4)% of Active NMT (b) (4)% of Active NMT (b) (4)% of Active NMT (b) (4)% of Active
pH (Potentiometric)	
Osmolality (Freezing Point Depression)	(b) (4) mOsm/kg
Appearance (Visual): Color Clarity Precipitate	 Colorless to Light Yellow (b) (4) NMT Ph. Eur. II None
Particulate Matter by HIAC	Meets USP Requirements NMT (b) (4) particles/mL ≥10µm NMT (b) (4)particles/mL ≥25µm NMT (b) (4)particles/mL ≥50µm
Sterility, Contents[d]	Meets USP Requirements
Sterility, Exteriors[d]	Meets USP Requirements

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

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 unpublished guidance (1978) and ocular safety of proposed acceptance limits is characterized in the published articles cited.

NDA 208135
Deputy Division Director Review
Wiley A. Chambers, MD

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

DRUG SUBSTANCE

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

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		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)				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) ((b) (4)		(b) (4) Finished drug product (b) (4) sterilizer	Process related impurities/ degradents (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
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, muti-surgeon, controlled study	to compare the clinical efficacy of lidocaine 2% with tetracaine 0.5% for cataract surgery	122	lidocaine 2% tetracaine 0.5%	No (Ocusoft)
					(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	5	4				4					3	2	22
General disorders and administra	Drug effect decreased						1		1							2
	Drug ineffective			1	1	2		1	2					2	1	10
	No adverse event		1													1
General disorders and administration site conditions Total			1	1	1	2	1	1	3					2	1	13
Immune system disorders	Hypersensitivity									1					1	2
Immune system disorders Total										1					1	2
Infections and infestations	Endophthalmitis												3	7		10
Infections and infestations Total													3	7		10
Injury, poisoning and procedural	Circumstance or information capable of leading to medication error										1	1				2
	Off label use													4		4
	Toxic anterior segment syndrome												15	11	2	28
Injury, poisoning and procedural complications Total											1	1	15	15	2	34
Investigations	Heart rate increased														1	1
	Oxygen saturation decreased													1		1
Investigations Total														1	1	2
Nervous system disorders	Headache														1	1
	VIIth nerve paralysis			1												1
Nervous system disorders Total				1											1	2
Grand Total		1	4	7	5	2	1	1	7	1	1	1	18	29	8	86

Serious post-market adverse events 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.

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

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/s/

WILEY A CHAMBERS
02/26/2016