CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208135Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Renata Albrecht, MD
Subject	Division Director Summary Review
NDA/BLA #	NDA 208135
pIND	pIND 115866
Applicant	Alcon Research, Ltd.
Date of Submission	April 30, 2015
PDUFA Goal Date	February 29, 2016
Proprietary Name / Non-Proprietary Name	N/A Tetracaine Hydrochloride Ophthalmic Solution 0.5%
Dosage Form(s) / Strength(s)	0.5%
Applicant Proposed Indication(s)/Population(s)	For procedures requiring a rapid and short-acting topical ophthalmic anesthetic
Action	*Approval*
Approved/Recommended Indication/Population(s) (if applicable)	For procedures requiring a rapid and short-acting topical ophthalmic anesthetic

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Jennifer Harris, William Boyd 1/20/2016
Statistical Review	Abel Eshete, Yan Wang 1/21/2016
Pharmacology Toxicology Review	Aaron Ruhland, Lori Kotch 1/26/2016, 2/25/2016
OPQ Review**	Anamitro Banerjee 1/25/2016, 2/26/2016
Clinical Pharmacology Review	Yongheng Eric Zhang, Phil Colangelo 10/13/2015
OPDP	Meena Ramachandra 1/27/2016
OSI	N/A
CDTL Review	William Boyd 2/29/2016
Deputy Director Review	Wiley Chambers 2/29/2016
OSE/DEPI	NA
OSE/DMEPA label review	Michelle Rutledge, Yelena Maslov 1/12/2016
ADL review	Jin Chen 2/26/2016
OSE/DRISK	NA
Project Manager	Eithu Lwin, Judit Milstein

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
**OPQ review includes drug substance, drug product, manufacturing process, microbiology, facility and biopharmaceutics.

Table of Contents

1. Benefit-Risk Assessment

All disciplines recommend approval of the application and/or defer to clinical for interpretation of the findings from clinical studies and presence of impurities exceeding ICH recommended levels. I have addressed these issues in the review that follows, and agree the application will be approved.

See Benefit –Risk Table summary below

Benefit-Risk Summary and Assessment

Tetracaine hydrochloride ophthalmic solution 0.5% (tetracaine) is a topical short-acting ophthalmic anesthetic that has been marketed by Alcon since 1959, whose manufacturing process has been essentially unchanged since 1996 and whose utilization for the past 15 years consists of an average of (b) (4) vials per year. This anesthetic is for use in the office, clinic or operating room for various examinations, procedures and surgeries involving the anterior segment and performed by ophthalmologists. Tetracaine is administered as a single drop, and may be repeated depending on the type and duration of procedure. This 505(b)(2) application relied on published literature for efficacy and safety; two of the 16 studies reviewed cited the Alcon products. The efficacy was demonstrated in studies where the patient served as a historical control (compared to their baseline sensitivity), tetracaine reduced corneal sensitivity as part of its anesthetic effect. In other studies, tetracaine was compared to another anesthetic, and demonstrated a reduction in the pain score after administration of the drop; this reduction in sensitivity enabled the ophthalmologist to perform the examination or surgery in the study population, ranging from tonometry, intravitreal injection, and cataract surgery. The anesthetic effect occurs in about 10-20 seconds and lasts approximately 10-20 minutes. Safety data were reported in some individual controlled clinical studies, from review articles, and from MedWatch forms. Risks following inappropriate use and associated complications or damage to the cornea are included in the Warnings and Precautions section of the prescribing information. The most common adverse reactions are stinging and pain on instillation, before the onset of anesthesia. The product offers another option in addition to currently available lidocaine and proparacaine topical ophthalmic solutions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Patients undergoing certain procedures on the eye such as measurement of intraocular pressure (tonometry), removal of foreign bodies and sutures from the cornea, conjunctival scraping in diagnosis and gonioscopic examination need short-term topical anesthesia for successful completion of the procedure; short-acting topical anesthesia is also indicated prior to surgical operations such as cataract extraction.	Published studies evaluated patients undergoing some of these procedures.
Current Treatment Options	Currently available topical anesthetics include Alcaine (proparacaine hydrochloride ophthalmic solution) 0.5%, ANDA 080027 and other generics, as well as Akten (lidocaine ophthalmic solution) 3.5%, NDA 022221.	Tetracaine offers another option for short-acting topical anesthesia.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Tetracaine Hydrochloride Ophthalmic Solution 0.5% STERI-UNIT is a sterile, preservative free formulation of tetracaine, marketed as an unapproved drug in the U.S. by Alcon, Inc., since 1959. It has been used for procedures requiring a rapid and short-acting topical ophthalmic anesthetic. The onset of action is approximately 10-20 seconds after instillation and lasts for 10-20 minutes. This 505(b)(2) application included published clinical studies (including adequate and well controlled studies) that demonstrate tetracaine's role as an anesthetic; two of these studies specifically cite the Alcon product.	According to Alcon Research, Ltd., they have been manufacturing and marketing tetracaine hydrochloride ophthalmic solution 0.5% since 1959, and their manufacturing currently has been unchanged since 1996.
Risk	The adverse events associated with labeled use are non-serious and mostly relate to the burning, stinging, discomfort and pain felt on instillation of the drop. This pharmacodynamic (anesthetic) effect of tetracaine is generally noted 10-20 seconds after instillation and lasts 10-20 minutes.	Most adverse events consist of stinging, burning, discomfort or pain due to irritation when the drop is instilled, and are transient
Risk Management	Warnings in labeling indicate that the eye should not be touched while anesthetized to prevent corneal injury. Additional warnings include the reported complications that occur with inappropriate use, such as the potential for endothelial injury after intracameral use and corneal epithelium lesions associated with chronic topical administration, neither use labeled.	Warnings and precautions about the action of the anesthetic, and inappropriate or inadvertent off-label use are included in the package insert.

2. Background

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. According to Alcon, the product has been marketed since 1959, and the product marketed currently has been manufactured essentially using the same method since 1996. (See section 3). Although there are currently no approved tetracaine ophthalmic products, two dermatologic tetracaine products are approved for marketing (NDA 21717 and NDA 21623).

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 115866 meeting was held with the Agency for this product in April 2013, during which agreement was reached that published nonclinical and clinical study reports would be submitted in this 505(b)(2) application. Alcon has not requested to rely on findings of safety and effectiveness of an FDA-approved tetracaine product.

Tetracaine is intended for use in procedures requiring a short-acting topical ophthalmic anesthetic such as during cataract surgery, tonometry, and removal of foreign body from the cornea. The dose is one drop instilled topically to the cornea. The current product is amendable for use in the office, clinic or operating room because the product and container are both sterilized.

Topical ophthalmic anesthetics currently approved are Akten (licocaine) 3.5% and proparacaine 0.5% (ANDA 40074, ANDA 40277, ANDA 80027, NDA 87681). Tetracaine provides another option.

3. Product Quality

Tetracaine Hydrochloride is a compendial drug substance and is described in the US Pharmacopeia. It is manufactured by (b) (4) under DMF (b) (4), and tested by multiple methods to confirm that it has the correct chemical structure, complies with applicable standards and acceptance criteria. Tetracaine hydrochloride is chemically designated as benzoic acid, 4-(butylamino)-,2-(dimethylamino) ethyl ester, monohydrochloride. Its chemical formula is $C_{15}H_{24}N_2O_2 \cdot HCl$. Tetracaine hydrochloride is a fine, white, crystalline, odorless powder and has a molecular weight of 300.82.

The tetracaine hydrochloride drug product is manufactured by Alcon, and in addition to the active ingredient, tetracaine hydrochloride 0.5% w/v (equivalent to 0.44% w/v tetracaine), includes sodium acetate as a (b) (4), sodium chloride as a (b) (4), acetic acid (b) (4) as a pH adjustor, and water for injection as (b) (4). Tetracaine Hydrochloride Ophthalmic Solution 0.5% has a pH of 3.7 to 5.5.

Based on 24-month stability testing, two impurities were identified in the drug product that exceeded the (b) (4)% levels (approximately (b) (4) µg/day based on (b) (4) mg bilateral dose) as recommended by ICH Q3B(R2). These are the (b) (4) formed

during the [redacted] and [redacted] a degradant; the applicant proposed specifications at [redacted]% and [redacted]% of active, respectively. These impurities were identified using a newly developed HPLC method, which was not used historically. The impurities were not qualified in nonclinical studies and were believed to have been present historically. At the Division's request as part of the review, the applicant provided a summary of manufacturing changes since 1996 when the [redacted] sterilization method was last changed from [redacted]. The Chemistry reviewers reviewed the history of the formulation, the manufacturing process, the key process parameters and controls for [redacted] sterilization of blister packs and concluded that the processes for the proposed drug product are [redacted] those of the historically marketed commercial product. Furthermore, several batches near expiry were tested using the new HPLC method, and corroborated that these two impurities were at similar levels. Taken together, the consistency in the manufacturing process and confirmation of these impurities using the new HPLC method at concentrations above [redacted]% indicate they have most likely been present in the marketed product at comparable levels historically. The applicant therefore has proposed to update their Drug Product specifications as listed below, as amended February 25, 2016, in the NDA.

Table 3.2.P.5.3–1 Regulatory Acceptance Specifications for Tetracaine Hydrochloride Ophthalmic Solution, 0.5% (FID 94152)

Test	Specification
Tetracaine Hydrochloride Identity (HPLC) [a]	Positive
Tetracaine Hydrochloride Identity (TLC) [a]	Positive
Tetracaine Hydrochloride Assay (HPLC)	90 to 110% Label
Tetracaine Hydrochloride Impurities (HPLC) [b] [redacted] Any Single Unspecified Impurity [c] Total Impurities	 NMT [redacted]% of Active [redacted]% of Active NMT [redacted]% of Active NMT [redacted]% of Active NMT [redacted]% of Active NMT [redacted]% of Active
pH (Potentiometric)	3.7 – 5.5
Osmolality (Freezing Point Depression)	[redacted] mOsm/kg
Appearance (Visual): Color Clarity Precipitate	 [redacted] NMT Ph. Eur. II None
Particulate Matter by HIAC	Meets USP Requirements NMT [redacted] particles/mL ≥ 10µm NMT [redacted] particles/mL ≥ 25µm NMT [redacted] particles/mL ≥ 50µm
Sterility [d]	Meets USP Requirements

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

The acceptability (qualification) of these limits for the [redacted] and [redacted] is discussed in Section 8.

Additionally, as noted in the pharmacology/toxicology review, the applicant has proposed the following drug product acceptance limits for [redacted]

The pharmacology/toxicology reviewer notes that while [redacted] is considered a mutagen, the single use of the drug product as prescribed mitigates concern over potential carcinogenicity. The applicant referenced published articles and [redacted] on [redacted] in drugs and devices. The maximum total daily intake of these impurities falls below limits set in the [redacted] and the references published articles establish ocular safety for proposed acceptance limits. Testing of historically marketed batches showed [redacted] and [redacted] concentrations which reasonably approximate the acceptance limits. To date, no adverse events have been reported with Tetracaine Ophthalmic Solution 0.5% which were attributable to the [redacted] within the drug product.

Tetracaine Hydrochloride Ophthalmic Solution, 0.5% is supplied in a medium density natural polyethylene (MDPE) round bottle with a natural low density polyethylene (LDPE) [redacted] tip dispensing plug and polypropylene (PP) closure. The product has a 4 mL fill in 4 mL configuration and blister packed. As noted above, the bottle and plug components are sterilized by [redacted], and the closure is [redacted]. The filled bottle with plug and closure are sealed into the blister [redacted]. Tamper evidence is provided by the heat sealed Tyvek backing on the blister.

The final recommendation from facilities inspections for the drug substance and drug product was acceptable on 12/11/2015.

The CMC review team recommends approval of the product.

4. Nonclinical Pharmacology/Toxicology

This 505(b)(2) application relied on published literature for nonclinical information.

The Pharmacology/Toxicology reviewer summarized that the applicant referenced published nonclinical studies which characterized tetracaine safety pharmacology, ocular absorption properties, effect on tear dynamics and effect on intraocular pressure. In dogs, intravenously administered tetracaine hydrochloride decreased blood pressure, heart rate, cardiac output, and stroke volume at a dose of 10 mg/kg and increased pulmonary arterial pressure at a dose of 9 mg/kg. Intravenously administered tetracaine hydrochloride, at a dose of 3 mg/kg, induced convulsions in dogs. Ocular effects following topical instillation described in the referenced

studies include a temporary decrease in intraocular pressure and reduced tear production and turnover. No other ophthalmic toxicity was reported.

The published literature did not include animal development and reproductive toxicology studies, or effects on fertility. Studies to assess the genotoxicity of tetracaine hydrochloride have not been reported in the published literature. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of tetracaine hydrochloride.

However, as discussed in Section 8, there is clinical experience with tetracaine ophthalmic solution products since approximately 1959 as a local anesthetic for procedures requiring a rapid and short-acting topical ophthalmic anesthesia. Alcon has provided a summary of manufacturing history for the past 20 years and data on utilization for the past 15 years of the Alcon product. Published controlled clinical trials, review articles and other marketing data provide information on the adverse event profile of the product and serve to characterize the reasonable safety of tetracaine when used for the intended purpose.

Alcon included a copy of a redacted pharmacology/toxicology review of another tetracaine NDA along with literature publications in their NDA 208135. On February 26, 2016, Alcon amended Sections 2.4, 2.6.6., and 2.6.7. to clarify that the application only relied on published studies and not on the findings of safety and effectiveness from an FDA-approved product.

The Pharmacology/Toxicology review team recommends approval.

5. Clinical Pharmacology

This 505(b)(2) application relied on published literature for clinical pharmacology information. 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. Tetracaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses thereby affecting local anesthesia.

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

Pharmacodynamic studies have not been conducted for this product by the applicant; however, prior studies have studied the duration of anesthesia for tetracaine. Identified studies include Bartfield 1994 in which the 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. In clinical practice, the duration of onset is seen 10-20 seconds after instillation and lasts between 10-20 minutes.

The Clinical Pharmacology review team recommends approval.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical-Efficacy

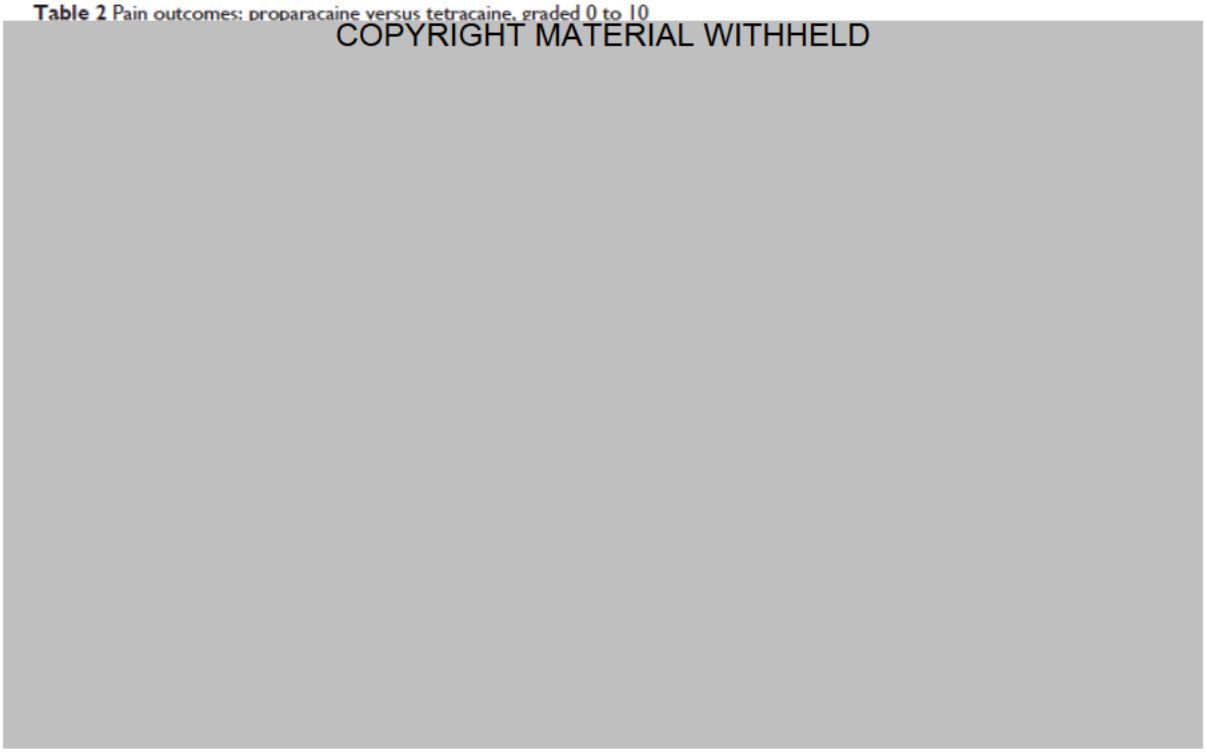
This is a 505(b)(2) application and relied on published clinical studies (including adequate and well controlled studies) of tetracaine hydrochloride ophthalmic solution, including two that specifically named the Alcon product. Other publications described studies using products from other manufacturers' products or did not state the source of the drug product. After a preliminary review of the studies, the applicant was asked to identify and submit additional publications and the review team conducted an independent search of the literature to augment the publications available for review.

In all, 16 clinical studies, including 4 clinical studies in pediatric patients, were reviewed for this application (see Appendix A). Two publications for support of efficacy and safety for tetracaine hydrochloride ophthalmic solution 0.5% specify the Alcon product (Moshifar 2014 and Rifkin 2012). In other publications, the drug source is not specified or the unapproved product is manufactured by a company other than Alcon. These publications of 0.5% and 1% tetracaine hydrochloride were also reviewed, given they contained the same active ingredient, mostly at the same concentration, which is a scientifically relevant consideration. The summaries of these studies below are derived from the CDTL review.

Moshifar 2014 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 the first eye or proparacaine in the first eye. 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. The outcome is shown in Table 2 from the publication (below).

In all patients, the tetracaine 0.5% patients had a higher pain score on instillation than proparacaine patients (3.2 vs. 1.1) which is statistically significant and a recognized adverse reaction to instillation of tetracaine. Once the anesthetic onset of action occurs, the results show that the pain scores during surgery and immediately post-surgery appear similar between the products. Tetracaine is then statistically superior to proparacaine in pain 30 minutes postoperatively, which may be due to shorter duration of pain control for proparacaine, an FDA approved product for topical short-term anesthesia. No difference in pain scores is seen at day 1 post-operatively.

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



Rifkin 2012 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 tetracaine 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. As shown in the table below, subjects who received tetracaine ophthalmic

solution reported the lowest pain score. The authors report that tetracaine is statistically superior to the comparator arms as noted below, although this difference may not necessarily be clinically meaningful. What is clinically meaningful is that the pain score is comparable and not higher than proparacaine (approved drug).

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.

The following studies used other sources of tetracaine hydrochloride:

Challam 2009 compared lidocaine 2% with tetracaine 0.5% (Tetravisc Ocusoft product) 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. The visual analog pain score was lower for the tetracaine compared to the lidocaine 2% (0.7% vs 1.8%). The Tetravisc product (unapproved) has a different formulation compared to Alcon product, and the approved lidocaine product has a concentration of 3.5%. Nevertheless, results indicate that both products were associated with an anesthetic effect based on the low pain scores.

Barequet 1999 compared the efficacy of a single application of lidocaine 2% gel with tetracaine 0.5% drops (manufacturer unknown) 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. In this study, the corneal sensation pre-operatively was 5-6 on a scale of 0-6, and when assessed at 5 minutes post drop and post-operatively, the score was zero. In this historically controlled study (patient acting as his/her control), the significant change (reduction) in sensation at 5 minutes is attributable to the anesthetic effect of the drug, and would be extremely unlikely if not impossible to occur spontaneously in 13 and 12 patients, respectively.

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)

(b) (4)

Shafi 1998 was conducted to evaluate discomfort with topical proxymetacaine 0.5% on instillation by comparing it against topical amethocaine 0.5% (another name for tetracaine, manufacturer unknown). 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. The results showed that on instillation, tetracaine had more reports of mild/moderate/severe pain compared to proxymetacaine. Successful tonometry was possible in 98% (n=52) and 93% (n=49%) patients, respectively. This would not have been expected if the patient's eye had not achieved anesthesia.

Watson 1991, Carden 1998, Kim 2003, Anninger 2007 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% (manufacturers were not specified in the publications). 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 efficacy 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.

Castellanos 2013 an additional pediatric study, assessed pain in premature infants treated with intravitreal antiangiogenic therapy for retinopathy of prematurity under topical anesthesia.

Additional studies are summarized in Medical Officer and CDTL review, and generally report results consistent with those summarized above. (See Appendix C)

Based on the Statistical Review, there are some limitations to the statistical interpretation of the studies. The following excerpt provides a summary of the issues:

Nine published studies were examined by the Statistical reviewer. Because the published studies used slightly different scales for pain measurement and evaluated different dosing regimen of tetracaine 0.5% in patients undergoing different procedures, the reviewer did not perform a formal meta-analysis. Three publications (Moshirfar 2014, Chalam 2009 and Rifkin 2009), in which a total of 209 subjects received at least one dose of tetracaine 0.5%, reported a statistically significant efficacy results for tetracaine 0.5%. However, the results in two of these publications (Rifkin 2009 and Moshirfar 2014) should be interpreted with caution because the results in Moshirfar 2014 were not adjusted for multiple comparisons, and the reviewer's analysis of the data from Rifkin 2009 did not show statistically significant results for the pairwise comparison of tetracaine 0.5% to the other treatment groups. For the reasons briefly summarized above, the evaluation of the clinical relevance of the study findings was deferred to the clinical reviewers.

As summarized and discussed above, tetracaine hydrochloride ophthalmic solution 0.5% is administered as a single drop (although more than one drop may be used by optometrists or ophthalmologist depending on the type and duration of procedure); it is for use as a short-acting local topical anesthetic for various examination and surgical procedures on the anterior segment. In these studies, as most directly illustrated by the Berequet 1999 study, the short-term anesthetic effect of tetracaine (and other anesthetics) was demonstrated by the reduction in patient corneal sensitivity from the baseline score so that various surgical or examination procedures can be conducted. This type of study is a historically controlled study where the patient acts as their own control and demonstration of an anesthetic effect is extremely unlikely if not impossible to occur spontaneously. The reduction in the pain score (on a scale of 0-10) is shown also in the Moshifar 2014 study at different time points from drug instillation, during surgery and after surgery, and similarly the anesthetic effect is demonstrated in the Rifkin 2012 study. These trials report the efficacy of the Alcon product, while additional published literature corroborates these findings with products where the manufacturer is not specified or a different manufacturer makes the product (unapproved drug). Given information on utilization data, the Alcon product is marketed primarily in the US and represents 30 to 80% of the market, depending on the source of information. Of note, among the submitted MedWatch forms, there have been reports of lack of efficacy, generally addressed by the health care provider by using additional product or changing product.

The clinical reviewer, CDTL and Deputy Division Director recommend approval, the Statistical reviewer defers to clinical for interpretation of some of the study data.

8. Safety

No clinical studies were conducted by Alcon, therefore the evaluation of safety is based on published literature and post-marketing reports. This includes two studies which identify the Alcon product and include 188 patients. In Moshirfar 2014, 128 patients and 256 eyes were evaluated, in the Rifkin study, 60 patients received 5 injections needing anesthesia so 100 injections were evaluated in 20 patients administered tetracaine. The recommended dosing is one drop to the eye; however, additional drops are sometimes given if adequate anesthesia has not been induced. Doses in the studies ranged from one to three drops.

The safety data available for review do not allow for a quantitative determination of the exact incidence of each type of adverse events. The adverse event profile for tetracaine based on the published studies suggests 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. Moshirfar 2014 (and Shafi 1998) noted pain on instillation of the anesthetic drop.

Toxicity related to inappropriate use has also been reported: Corneal toxicity with damage to the epithelium occur with chronic use/abuse of anesthetics which is rare since patients are normally not prescribed these drops for self-administration. There are also reports of endothelial cell toxicity when the drug is injected intracamerally, into the anterior chamber of the eye.

Due to limited or lacking adverse event reporting in published controlled studies, two review articles on the toxicity of topical anesthetics Havener 1983 and McGee 2007 and an article by Rosenwasser 1990, were submitted and provided a qualitative overview of adverse events:

- Patients receiving topical administration of tetracaine eye drops may report *burning sensation* of about 30 seconds, also described as *stinging* and *discomfort* in the affected eye. Patients will typically experience *numb sensation* in the instilled eye ranging in duration from 10 to 20 minutes depending on dosage (number of drops).

- Repeated administration of tetracaine anesthetic has the potential to cause superficial *corneal epithelial lesions*; therefore, it is recommended that tetracaine not be prescribed for patient home-use. 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. Longterm use is not recommended; Rosenwasser 1990 reported cases of *corneal ulceration, thinning and perforation*, some requiring full thickness corneal transplantation with long term abuse.

- In rare cases, tetracaine may cause *allergic contact dermatitis* after repeated use.

- Physicians are warned not to hyperdermically inject tetracaine solution for ophthalmologic procedures as cases of *death* have been reported.

- Systemic side effects associated with topical ophthalmic anesthetics have also been reported, including *anxiety*, *shortness of breath*, and *seizure*.

As noted, Alcon has marketed tetracaine hydrochloride ophthalmic solution 0.5% since 1959, and the current product has been manufactured using essentially the same method since 1996. The applicant also provided information on the marketing of the product, indicating that since about 2002, over (b) (4) vials are marketed annually in the United States, with smaller numbers before that time. Alcon submitted 86 MedWatch forms for their unapproved product which included reports of adverse reactions associated with installation as described above,

along with some reports of lack-of–efficacy that were addressed by giving additional drops or using a new bottle. (See Appendix B) Other events such as toxic anterior segment syndrome (TASS) and endophthalmitis were reported for patients undergoing cataract surgery – these cases sometimes occurred in clusters and patients received multiple medications peri-operatively. These cases were usually investigated, changes were made (e.g., new procedures for cleaning instruments) and when follow up was available, further TASS cases were not seen; the reports did not conclude that tetracaine was the causative factor.

In the original proposed labeling, there was a statement about a (b) (4) (b) (4), which had been present in labeling of the unapproved drug. However, this was based on a single publication concerning an unusual reaction to a formulation of proparacaine (containing (b) (4) which is no longer marketed. Among the 86 MedWatch forms, one cited (b) (4) but upon review of the submitted text, lidocaine testing was negative and Solumedrol was implicated in the report. The applicant reported that they adopted the (b) (4) labeling from the (b) (4) product. The Division found that similar labeling was included in the Federal Register notice published in 1969 of a DESI review for two other local topical anesthetics (b) (4)

The Medical Officer, CDTL and Deputy Division Director recommend approval.

9. Advisory Committee Meeting

This application did not raised new scientific issues that needed input from the Advisory Committee.

10. Pediatrics

The application was discussed at the January 20, 2016, Pediatric Review Committee (PeRC) meeting and the committee agreed that full pediatric assessment is based on published literature (including adequate and well-controlled trials) in pediatric patients as well as uncontrolled data on use of tetracaine as a topical ocular anesthetic in infants with retinopathy of prematurity.

11. Other Relevant Regulatory Issues

This is a 505(b)(2) application that relied on published literature for nonclinical and clinical studies. The product is a solution, and has been marketed by Alcon since 1959. One issue raised in the application is the presence of 2 impurities related to the sterilization process of tetracaine with (b) (4). These impurities exceed ICH recommended limits of (b) %, and nonclinical studies were not conducted to qualify these impurities. Therefore, the applicant was asked to provide evidence that their product historically contained these impurities and was not associated with unexpected toxicities related to their presence. Alcon stated that

impurities were not historically measured, but was able to provide information that their manufacturing process has not essentially unchanged since 1996 and provided impurity testing on batches of expired/near expired product confirming the presence of these 2 impurities to substantiate this statement. The CMC reviewers concluded that based on this information, it is reasonable to conclude that the product, and therefore other characteristics such as the impurities are have been in the marketed product.

The applicant provided information on their examination of these impurities using Derek Nexus system (Derek KB 2014 1.0, DEREK NVS 42.5). As Alcon reported, this database and search engine considers the potential for effects on all organ systems, including ocular, developmental toxicity, carcinogenicity, sensitization, and mutagenicity. For (b) (4) no structural alerts were identified for any potential toxicity (Derek Nexus Report – (b) (4). For the (b) (4), two alerts were identified, phospholipidosis and carcinogenicity, both were identified as "plausible" by the system (Derek Nexus Report – (b) (4)). The alerts are based on substructures within the (b) (4) which would require breakdown of the parent molecule. The risk of systemic effects is further mitigated by the expected low systemic exposure following topical ocular dosing (typically 1 to 10% bioavailability [(b) (4) In conclusion, although two of the impurities are above the qualification threshold described in the ICH Q3B(R2) Guideline for Impurities in New Drug Products, no additional health risk is assumed based on the nonclinical risk assessment, the short-term, single-use clinical indication of this product, and the long history of safe clinical use; presumably with product containing the (b) (4) /impurities.

To support the above conclusion, the applicant provided utilization data demonstrating that over (b) (4) vials are distributed annually since 2002. Other information suggests that the Alcon product represents 30 to 80% of the market, and as already discussed, this product when used on label is given as one drop (possible more depending on the type and duration of procedure) by an optometrist or ophthalmologist to induce short-term local topical anesthesia during examinations or surgical procedures. Adverse reactions that might occur would be reported by the patient (as they are following instillation) and observed by the ophthalmologist. In the Derek analysis above, there was no toxicity signal for (b) (4) while phospholipidosis and carcinogenicity were potential signals for the (b) (4). The development of phospholipidosis in the cornea would be an observable finding, and carcinogenicity with single topical drops is highly unlikely, and would be more likely to be reported with chronic use or other routes. Although it is difficult to prove a negative, the absence of reports that might indicate attributable toxicity to the (b) (4) can reasonably serve to qualify these components of the drug product at 24-months.

12. Labeling

The **INDICATIONS AND USAGE** section in **HIGHLIGHTS OF PRESCRIBING INFORMATION** will include the established pharmaceutical class for tetracaine: an ester local anesthetic.

Link to established pharmaceutical class text page:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM428333.pdf

The **FULL PRESCRIBING INFORMATION** portion of labeling will include the following text in Section 1 and 2.

> **1 INDICATIONS AND USAGE**
> Tetracaine Hydrochloride Ophthalmic Solution 0.5% is indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic.
>
> **2 DOSAGE AND ADMINISTRATION**
> **2.1 Topical Administration**
> One drop topically in the eye as needed. Discard unused portion.
> **2.2 Sterile Field Administration**
> Open package using standard aseptic technique. The DROP-TAINER® dispenser may then be allowed to fall upon a sterile surface. The entire outer surface of the DROP-TAINER® dispenser and its contents are sterile.

The proposal to include a Contraindication of (b) (4) presumably based on a pre-1969 report of a (b) (4) whose description sounded similar to an adverse reaction reported in the 1969 FR Notice for the DESI review of two other topical anesthetics, (b) (4). A reasonably detailed review of the literature by the applicant and the review team was not able to identify cases of tetracaine causing this reaction; even reports of (b) (4) were either from other routes/sites or due to another drug.

The Warnings include information on adverse reactions associated with inappropriate use (chronic administration, intracameral administration), and caution about the eye's insensitivity when anesthetized.

Adverse Reactions includes reports of stinging on instillation, reported in the literature and post-marketing.

The labeling notes that some of the usual animal studies in development have not been done, but as discussed in Section 8, the long and broad use of Alcon's product (marketed since 1959, manufacturing process essentially unchanged since 1996, 15 years of marketing experience with an average of over (b) (4) vials per year), provides reasonably abundant information on clinical experience in patients with this short-acting anesthetic.

13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

Not applicable

- Other Postmarketing Requirements and Commitments

Not applicable

APPENDIX A: List of Published Clinical Studies (Source: Medical Officer Review)

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- 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 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	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

		strabismus surgery in children			
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
Sabermogha dam 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.

APPENDIX B: Postmarketing adverse events

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

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**

Source – Medical Officer Review (Ref 2.7.4. Summary of Clinical Safety, Table 2.7.4.7-1)

APPENDIX C: References

The following references were reviewed by the Medical Officer and CDTL during the review of NDA 208135 (source: Medical Officer Review and CDTL review)

Anninger W, Forbes B, Quinn G, Schreiner MS. The effect of topical tetracaine eye drops on emergence behavior and pain relief after strabismus surgery. JAAPOS. 2007:11(3):273–6.

(b) (4)

Barequet IS, Soriano ES, Green WR, O'Brien TP. Provision of anesthesia with single application of lidocaine 2% gel. J Cataract Refract Surg. 1999;25(5):626–31.

Bartfield JM, Holmes TJ. A comparison of proparacaine and tetracaine eye anesthetics. Acad Emerg Med. 1994; 1(4):364-367.

(b) (4)

Busbee, BG. Lidocaine hydrochloride gel for ocular anesthesia: results of a prospective, randomized study. Ophthalmic Surg Lasers Imaging. 2008 Sep-Oct;39(5):386-90.

Carden SM, Colville DJ, Davidson AJ, McKenzie IM, Mackey DA, McKenzie J, Elder JE. Adjunctive intra-operative local anaesthesia in paediatric strabismus surgery: a randomized controlled trial. Aust N Z J Ophthalmol. 1998; 26(4):289–97.

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

Chalam K, Murthy RK, Agarwal S. Comparative efficacy of topical tetraVisc versus lidocaine gel in cataract surgery. BMC Ophthalmology. 2009;9:7. doi:10.1186/1471-2415-9-7.

(b) (4)

Havener WH. Chapter 5: Anesthesia. In: Klein EA, ed. Ocular Pharmacology, 5th ed. St. Louis: The C.V. Mosby Company; 1983: 72–119.

Kim J, Azavedo L, Bhananker S, Bonn G, Splinter W. Amethocaine or ketorolac eyedrops provide inadequate analgesia in pediatric strabismus surgery. Can J Anaesth. 2003; 50(8):819–23.

McGee HT, Fraunfelder FW. Toxicities of topical ophthalmic anesthetics. Expert Opin Drug Saf. 2007; 6(6):637–40.

Moshirfar, M, Mifflin, MD, McCaughey, MV, et al (2014) Prospective, randomized, contralateral eye comparison of tetracaine and proparacaine for pain control in laser in situ keratomileusis and photorefractive keratectomy. Clinical Ophthalmology; 8:1213-1219.

Nomura k, Singer.Corneal sensation after topical anesthesia. Cornea. 2001; 20(2):191-203.

Rifkin, L and Schaal, S (2012) Factors affecting patients' pain intensity during in office intravitreal injection procedure. Retina; 32 (4):696-700.

Rosenwasser G, Holland S. Topical anesthetic abuse. Ophthalmology. 1990; 97:967-972

Sabermoghadam Ranjbar, AA, Rajabi, O, Salari, R, et al (2012) Lidocaine cyclodextrin complex ophthalmic drop, a new topical anesthetic choice. Iranian Red Crescent Medical Journal; 14 (9)

Sanabria, MR, Montero, JA, Losada, MV, et al (2013) Ocular pain after intravitreal injection. Current Eye Research; 38 (2):278-282.

Shafi, T and Koay, P (1998) Randomised prospective masked study comparing patient comfort following the instillation of topical proxymetacaine and amethocaine. British Journal of Ophthalmology; 82 (11):1285-1287.

Than TP, Bartlett JD. Chapter 6: Local Anesthetics. In: Clinical Ocular Pharmacology, 5th ed. Butterworth-Heinemann Elsevier; 2007: 85-95

Tsoumani AT, Asproudis IC, Damigos D. Tetracaine 0.5% eyedrops with or without lidocaine 2% gel in topical anesthesia for cataract surgery. Clin Ophthalmol. 2010; 4:967–70.

Watson DM. Topical amethocaine in strabismus surgery. Anaesthesia. 1991; 46(5):368–70.

Yu CB, Wong VW, Fan DS, Yip WW, Lam DS. Comparison of lidocaine 2% gel versus amethocaine as the sole anesthetic agent for strabismus surgery. Ophthalmology.2003; 110(7):1426–9.

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

/s/

RENATA ALBRECHT
02/29/2016