

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208135Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 208135
Supporting document/s: N001, N014
Applicant's letter date: 4-30-2015
CDER stamp date: 4-30-2015
Product: Tetracaine hydrochloride ophthalmic solution
0.5%
Indication: For procedures requiring a rapid and short-
acting topical ophthalmic anesthetic
Applicant: Alcon Research Ltd
6201 South Freeway
Fort Worth, TX 76134
Review Division: Division of Transplant and Ophthalmology
Products
Reviewer: Aaron Ruhland, PhD
Supervisor/Team Leader: Lori Kotch, PhD, DABT
Division Director: Renata Albrecht, MD
Project Manager: Eithu Lwin

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1 Executive Summary

1.1 Introduction

This review serves as a revision of the full review submitted for this application (dated 1-25-2016, author: Aaron Ruhland). In this review, changes are made to the following sections:

- Section 1.1: Executive summary:
 - Remove statement describing (b) (4) of Tetracaine Hydrochloride Ophthalmic Solution 0.5%. (b) (4)
- Section 1.3.3.2: FDA version of the labeling*
- Section 2.7: Regulatory Background
 - Remove statement regarding (b) (4) of the drug product (b) (4)

*In the original NDA submission, the FDA revised labeling used information from the labeling for Pliaglis® (NDA 021717) to construct the labeling for the nonclinical sections of the labeling for this application. The applicant does not wish to rely on these data for the labeling of this drug product and has not formally referenced NDA 021717. Updates to the PI are supported by updates to nonclinical sections in Module 2.4 and 2.6 formally submitted by the sponsor on 2-24-16 (SD14). As such, the revised FDA labeling recommendations no longer contain information from the Pliaglis® labeling. No nonclinical data were found in the literature to describe the effects of tetracaine on developmental and reproductive toxicology, genotoxicity or carcinogenicity, and this information is reflected in the *revised FDA version* labeling recommendations presented in section 1.3.3.2 of this review.

These changes do not alter the approvability of this NDA from a Pharmacology/ Toxicology perspective.

1.3 Recommendations

1.3.1 Approvability: Approvable from a Pharmacology/Toxicology perspective

1.3.3 Labeling (Sections relevant to the Pharmacology/Toxicology discipline)

1.3.3.1 Former FDA version of the labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

There are no adequate and well-controlled studies with Tetracaine Hydrochloride Ophthalmic Solution 0.5% in pregnant women.

(b) (4)

(b) (4)

8.2 Lactation

Risk Summary

There are no data to assess whether Tetracaine Hydrochloride Ophthalmic Solution 0.5% is excreted in human milk or to assess its effects on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tetracaine Hydrochloride Ophthalmic Solution 0.5% and any potential adverse effects on the breastfed child from Tetracaine Hydrochloride Ophthalmic Solution 0.5% or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

(b) (4)

No human data on the effect of Tetracaine Hydrochloride Ophthalmic Solution 0.5% on fertility are available.

12.1 Mechanism of Action

Tetracaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses, thereby effecting local anesthesia.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been conducted to evaluate the carcinogenic potential of tetracaine hydrochloride.

(b) (4)

1.3.3.2 Revised FDA version:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with Tetracaine Hydrochloride Ophthalmic Solution 0.5% in pregnant women. Animal developmental and reproductive toxicity studies with tetracaine hydrochloride have not been reported in the published literature.

8.2 Lactation

Risk Summary

There are no data to assess whether Tetracaine Hydrochloride Ophthalmic Solution 0.5% is excreted in human milk or to assess its effects on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tetracaine Hydrochloride Ophthalmic Solution 0.5% and any potential adverse effects on the breastfed child from Tetracaine Hydrochloride Ophthalmic Solution 0.5% or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

No human data on the effect of Tetracaine Hydrochloride Ophthalmic Solution 0.5% on fertility are available.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of 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.

Animal studies to assess the effects of tetracaine hydrochloride on fertility have not been reported in the published literature.

2.7 Regulatory Background

Tetracaine Hydrochloride Ophthalmic Solution 0.5% has been marketed in the United States by the Applicant since 1959.

11 Integrated Summary and Safety Evaluation

At internal meetings and discussions with the applicant, the intent to rely on (b) (4) (NDA 021717) was clarified, along with (b) (4) of the drug product. Updates to nonclinical sections in Module 2.4 and 2.6 were formally submitted by the sponsor on 2-24-16 (SD14), and the PI was revised accordingly. These changes do not affect the overall conclusion regarding approvability of the drug product from a Pharmacology Toxicology perspective.

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/s/

AARON M RUHLAND
02/25/2016

LORI E KOTCH
02/25/2016

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FOOD AND DRUG ADMINISTRATION
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PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Supporting document/s: N001
Applicant's letter date: 4-30-2015
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1 Executive Summary

1.1 Introduction

The applicant has submitted this New Drug Application in support of Tetracaine Hydrochloride Ophthalmic Solution, 0.5% by topical ophthalmic instillation for procedures requiring a rapid and short-acting topical ophthalmic anesthetic. Tetracaine is an ester-linked local anesthetic that prevents the generation and the conduction of nerve impulses. The drug product has been marketed in the United States for over 40 years (b) (4). The applicant has submitted this application as a 505(b)(2) with limited nonclinical data to support approval.

1.2 Brief Discussion of Nonclinical Findings

For pharmacology, safety pharmacology, general ADME, and toxicology, the applicant relies on the Agency's previous findings of safety for NDA 21-717 (Pliaglis; 7% tetracaine/7% lidocaine).

The applicant referenced published nonclinical studies which further 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.

Two impurities identified by the applicant are proposed at specifications which exceed those recommended in ICH Q3B(R2). (b) (4) (b) (4) are proposed with specifications at no more than (b) (4)% and (b) (4)%, respectively. These specifications exceed the ICH Q3B(R2) specification limits of no-more-than (NMT) 1.0% (approximately (b) (4) µg/day based on (b) (4) mg bilateral dose). There were no nonclinical data submitted to qualify these impurities above ICH recommended concentrations. The applicant stated that the formulation, manufacturing process, including key process parameters and controls for (b) (4) of blister packs for the proposed drug product are the same as those of the historically marketed commercial product. The applicant indicated that the release and stability specifications for the drug product are the same as those of the historically marketed commercial product, with the exception of impurity testing. Impurity concentrations were not historically tested. Therefore, no historical data regarding content of the proposed impurities in previously marketed clinical batches was provided. The applicant set the proposed product specifications for the impurities based on results from studies on three primary stability batches. As such, the product specifications may be supported

by historical clinical data, pending assessment of historic and current process comparability by the CMC team, and assessment of historic clinical data by the Clinical review team.

Additionally, the applicant has proposed the following drug product acceptance limits for

(b) (4). The applicant proposes the following acceptance limits:

(b) (4)

While (b) (4) is considered a mutagen, the single use of the drug product as prescribed mitigates concern over potential carcinogenicity. The applicant referenced published articles and (b) (4) on (b) (4) (b) (4) in drugs and devices. The maximum total daily intake of these impurities falls below limits set in the (b) (4) and the references published articles establish ocular safety for proposed acceptance limits. Testing of historically marketed batches showed (b) (4) 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 (b) (4) within the drug product.

1.3 Recommendations

1.3.1 Approvability: Approvable from a Pharmacology/Toxicology perspective

1.3.3 Labeling (Sections relevant to the Pharmacology/Toxicology discipline)

1.3.3.1 Applicant's version of the labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with Tetracaine Hydrochloride Ophthalmic Solution 0.5% in pregnant women.

(b) (4)
(b) (4)



(b) (4)

8.2 Lactation

Risk Summary



(b) (4)

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tetracaine Hydrochloride Ophthalmic Solution 0.5% and any potential adverse effects on the breastfed child from Tetracaine Hydrochloride Ophthalmic Solution 0.5% or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

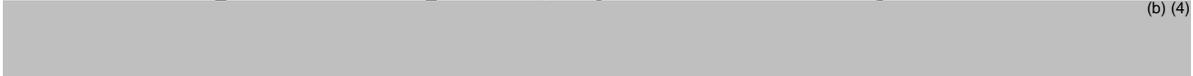
12.1 Mechanism of Action



(b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility



(b) (4)



1.3.3.2 Suggested FDA version (Redline: deletions noted as strikethrough font and additions are noted as **red double underlined font):**

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary



There are no adequate and well-controlled studies with Tetracaine Hydrochloride Ophthalmic Solution 0.5% in pregnant women.



(b) (4)

8.2 Lactation

Risk Summary

(b) (4) There are no data to assess whether Tetracaine Hydrochloride Ophthalmic Solution 0.5% (b) (4) is excreted in human milk; or to assess its effects on milk production/excretion. (b) (4)

(b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Tetracaine Hydrochloride Ophthalmic Solution 0.5% and any potential adverse effects on the breastfed child from Tetracaine Hydrochloride Ophthalmic Solution 0.5% or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

(b) (4)

No human data on the effect of Tetracaine Hydrochloride Ophthalmic Solution 0.5% on fertility are available.

12.1 Mechanism of Action

(b) (4)

(b) (4) Tetracaine blocks sodium ion channels required for the initiation and conduction of neuronal impulses, thereby effecting local anesthesia.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

2 Drug Information

2.1 Drug

CAS Registry Number: 136-47-0

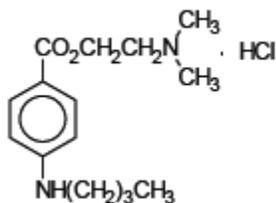
Generic Name: Tetracaine hydrochloride ophthalmic solution, 0.5%

Code Name: AL-15154A

Chemical Name: 2-(Dimethylamino)ethyl p-(butylamino)benzoate monohydrochloride

Molecular Formula/Molecular Weight: $C_{15}H_{24}N_2O_2 \cdot HCl$ / 300.82 g/mol

Structure:



Pharmacologic Class: Ester local anesthetic

2.2 Relevant INDs, NDAs, BLAs and DMFs

The applicant references:

- NDA 21-717: Pliaglis (7% lidocaine/7% tetracaine) indicated for local dermal anesthesia on intact skin for nonclinical findings of ADME, safety pharmacology, general toxicology, reproductive toxicology, genotoxicity and carcinogenesis. Approved June 29, 2006.

2.3 Drug Formulation

Table 1. Formulation of Tetracaine Ophthalmic Solution, 0.5%

Component	Concentration (% w/v)	Function
Tetracaine hydrochloride	0.5 (b) (4)	Active
Sodium acetate (trihydrate)	(b) (4)	(b) (4)
Sodium chloride		
Acetic acid (b) (4)	-to pH 4.5	pH adjustment
(b) (4)		
Water	(b) (4)	(b) (4)

(b) (4)

2.4 Comments on Novel Excipients

All excipients are qualified for topical ophthalmic use.

2.5 Comments on Impurities/Degradants of Concern

Drug Product Related Impurities

The applicant has identified two product related impurities which exceed ICH Q3B (R2) qualification threshold limits. The two impurities (b) (4) and (b) (4), are proposed at product specifications at no more than (NMT) (b) (4)% and (b) (4)%, respectively. These specifications exceed the ICH Q3B(R2) specification limits of NMT 1.0% (approximately (b) (4) µg/day based on (b) (4) mg bilateral dose).

The applicant used the Derek Nexus system (Derek KB 2014 1.0, DEREK NVS 42.5), an *in silico* assessment, to identify potential for effects on organ systems, including ocular, developmental toxicity, carcinogenicity, sensitization, and mutagenicity. For (b) (4) no structural alerts were identified for any potential toxicity. For the (b) (4) two alerts were identified, phospholipidosis and carcinogenicity; both were identified as “plausible” by the system. The alerts were 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. Further, the applicant justifies the higher concentrations of these impurities based on the short-term, single-use clinical indication of the product, and the long history of safe clinical use presumably with product containing the (b) (4) /impurities. In letters to the applicant dated 10-26-2015 and 11-24-2015, the Chemistry, Manufacturing and Controls (CMC) reviewer asked the applicant the following:

1. *Provide a comparison of your proposed drug product presentation with your historically marketed commercial product with regards to*
 - a. *Formulation, manufacturing process, including key process parameters and controls for (b) (4) sterilization of blister packs*
 - b. *Container closure system including type, fill volume, and materials of construction*
 - c. *Release and stability specifications, including tetracaine assay and impurities. Also include representative results of batch release and stability testing for your marketed product demonstrating that the impurities at the proposed levels are present in commercial circulation.*
2. *In your amendment dated November 13, 2015, you have indicated that the proposed drug product presentation and manufacturing process are the same (b) (4) those of the historically marketed commercial product. Provide analytical results from impurity testing of multiple lots of your historically marketed product to support the proposed drug product impurity specifications.*

In response (SDN006 and SDN007), the applicant stated that the formulation, manufacturing process, including key process parameters and controls for (b) (4) (b) (4) sterilization of blister packs for the proposed drug product are the same as those of the historically marketed commercial product. The applicant indicated that the release and stability specifications for the drug product are the same as those of the historically marketed commercial product, with the exception of impurity testing. Impurity concentrations were not historically tested. Therefore, no historical data regarding content of the proposed impurities in previously marketed clinical batches was provided. The applicant set the proposed product specifications for the impurities based on three primary stability batches.

No additional animal testing was performed to qualify the impurities. A consult was sent for Impurity QSAR analysis review (CDER/OTS/OCP/DARS). Resulted showed that based on the entire weight of evidence, the two degradants identified in NDA 208135 are predicted to be negative for bacterial mutagenicity (see APPENDIX A).

(b) (4) **Process Impurities**

Additionally, the applicant has proposed the following drug product acceptance limits for (b) (4) reaction products, (b) (4)

(b) (4). These (b) (4) are therefore considered qualified at the acceptance limits proposed by the applicant.

2.6 Proposed Clinical Population and Dosing Regimen

Tetracaine Hydrochloride Ophthalmic Solution 0.5% is indicated for procedures requiring a rapid and short-acting topical ophthalmic anesthetic. The dosing regimen is for “one drop topically in the eye(s), as needed” per Applicant’s proposed labeling.

The applicant defined the drop volume as 0.038 mL, therefore the total dose is 0.192 mg/drop or 0.384 mg/ dose, if administered bilaterally. This dose was used for determination of safety margins in the labeling and presumed that only a single drop per eye will be administered. The Applicant also describes a worse case dosing regimen as 3 – 5 doses. At 5 doses/eye, this would provide a maximum of 10 drops/day if administered bilaterally (0.96 mg/eye/day or 1.92 mg total daily dose). This dose is used for calculation of maximum daily intake of the (b) (4)

2.7 Regulatory Background

Tetracaine Hydrochloride Ophthalmic Solution 0.5% has been legally marketed in the United States by the Applicant since 1959 and by other manufacturers with an FDA status of “unapproved drug” (b) (4). With this submission the Applicant is seeking formal approval of the drug for its historic medical application in ophthalmological settings and will assume all of the regulatory obligations of an approved NDA.

3 Studies Submitted

3.1 Studies Reviewed

- Igarashi, H., 1984, “Studies on rabbit corneal permeability of local anesthetics (I)”, *Japan J Pharmacol*, 34: 429 – 434.
- Liu, P., *et al.*, 1982, “Acute cardiovascular toxicity of procaine, chloroprocaine, and Tetracaine in anesthetized ventilated dogs”, *Regional Anesth*, 7: 14 -19.
- (b) (4) Derek N3exus Report (reviewed via consult; see APPENDIX A)
- (b) (4) Derek Nexus Report (reviewed via consult; see APPENDIX A)
- Liu, P., *et al.*, 1983, “Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and Tetracaine in awake dogs following rapid intravenous administration”, *Anesth Analg*, 62: 375 – 379.
- Patton, T. and J. Robinson, 1975, “Influence of topical anesthesia on tear dynamics and ocular drug bioavailability in albino rabbits”, *J Pharm Sci*, 64: 267 – 271.
- Sarchahi, A. and H. Bozorgi, 2012, “Effect of tetracaine on intraocular pressure in normal and hypertensive rabbit eyes”, *J Ophthalmic Vis Res*, 7: 29 – 33.

3.2 Studies Not Reviewed

- AHFS: Drug Information 2012. Published by Board of the American Society of Health-System Pharmacists.
- Caterall, W., 2011. Goodman & Gilman's The Pharmaceutical Basis of Therapeutics, 12th edition > Section II. Neuropharmacology > Chapter 20. Local Anesthetics
- Chastain, J., 2003, Drugs and the Pharmaceutical Sciences: Ophthalmic drug delivery systems Part 3: General considerations in ocular drug delivery", Volume 130, 2nd edition
- Hino, Y., 2001, "Distribution of Tetracaine and its metabolite in rabbits after high versus normal spinal anesthesia", *Forensic Sci Int*, 124: 130 – 136.
- Le Guévello, P, *et al.*, 1993, "High-performance liquid chromatographic determination of bupivacaine in plasma samples for biopharmaceutical studies and application to seven other local anesthetics", *J Chromatogr*, 622: 284 – 290.
- Luo, A., *et al.*, 1991, "Ocular drug interaction involving topically applied timolol in the pigmented rabbit", *Curr Eye Res*, 10: 231 – 240.
- Woolfson, A., *et al.*, 1990, "The metabolism of amethocaine by porcine and human skin extracts: influence on percutaneous anesthesia", *Int J Pharmaceutics*, 62: 9 – 14.
- Woolfson, A., *et al.*, 1992, "Percutaneous penetration characteristics of amethocaine through porcine and human skin"
- Registry of toxic effects of chemical substances: Tetracaine, 2012

3.3 Previous Reviews Referenced

The Pharmacology/Toxicology review of Pliaglis® is publicly available through drugs@fda.gov (authors: R. Daniel Mellon, Ph.D., and Suzanne R Thornton-Jones, Ph.D, dated June 14, 2006).

4 Pharmacology

4.1 Primary Pharmacology

No new pharmacology studies with tetracaine hydrochloride were conducted by the Applicant for this application. When applied locally to nerve tissue in appropriate concentrations, tetracaine reversibly blocks action potentials that are typically responsible for nerve conduction. Tetracaine blocks conduction by decreasing or preventing the large transient increase in the permeability of the cell membrane to sodium ions that normally is produced during nerve signal propagation.

4.3 Safety Pharmacology

Safety pharmacology studies of tetracaine were not been conducted by the Applicant.

Liu, P., et al., 1982, "Acute cardiovascular toxicity of procaine, chlorprocaine, and Tetracaine in anesthetized ventilated dogs", *Regional Anesth*, 7: 14 -19.

The acute intravenous cardiovascular toxicity of tetracaine was determined in pentobarbitalized, ventilated dogs (n=5). The cumulative lethal dose was approximately 30 mg/kg. Significant depression of mean arterial blood pressure, heart rate, cardiac output and stroke volume was observed at 10 mg/kg. A statistically significant decrease ($p < 0.01$) in heart rate was observed at a cumulative dose of 19 mg/kg of tetracaine (Figure 1). The authors state that an initial increase in cardiac output and stroke volume of ~20% was seen with low doses. The actual doses which caused these increases were not defined, and these increases were not statistically significant. Statistically significant decreases ($p < 0.01$) in cardiac output and stroke volume occurred at 19 mg/kg of tetracaine.

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Statistically significant hypotension occurred at doses of 9 mg/kg of tetracaine ($p < 0.01$) (Figure 2). No significant change in total peripheral resistance was observed until the lethal dose was reached.

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Tetracaine produced a rise in both mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR; Fig. 3). The increase in PAP achieved statistical significance ($p < 0.01$) at a dose of 9 mg/kg. The authors state that peak increases in PVR of 279% were observed, but the dose which caused the effect was not defined (see Figure 3, below). A decrease in both parameters occurred only at the lethal dose.

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Reviewer's note: The total dose of 0.192 mg/eye/day or 0.384 mg/day total daily dose if administered bilaterally. The lowest dose of tetracaine which cause systemic cardiovascular or pulmonary effects in the dog was 9 mg/kg which represents a 760-fold margin based on body surface area (mg/m² basis) over 100% absorption of the recommended human ophthalmic dose (bilateral administration; presuming only a single drop per eye is administered to the patient).

Liu, P., et al., 1983, "Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and Tetracaine in awake dogs following rapid intravenous administration", *Anesth Analg*, 62: 375 – 379.

The toxicity of tetracaine was reported in awake dogs following rapid intravenous administration. Each animal received increasing serial intravenous doses of tetracaine at 30-min intervals. The dosing schedule of 1.0, 3.0, 5.0, 10.0, and 15.0 mg/kg was

terminated when frank seizure activity was observed. Additionally, animals were continuously observed for other signs of overt systemic effects such as tremor, salivation, sedation, muscular rigidity, and death. A mean dose of approximately 3 mg/kg tetracaine caused convulsions. The duration of convulsive activity was 5.2 ± 2.0 min. One animal which received 4 mg/kg tetracaine continued to convulse for 15 minutes, showed signs of respiratory and cardiac depression and ultimately died. The mean dose which caused irreversible cardiovascular depression and death was 26.9 mg/kg. The ratio of the convulsive dose to the dose causing cardiovascular depression was 6.7 indicating that the CNS is more sensitive to tetracaine toxicity than the cardiovascular system.

Reviewer's note: The dose which caused convulsions, 3 mg/kg, is approximately 250-fold higher than 100% absorption of the recommended human ophthalmic dose (bilateral administration; presuming only a single drop per eye is administered to the patient), on a mg/m² basis.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption

Igarashi, H., 1984, "Studies on rabbit corneal permeability of local anesthetics (I)", *Japan J Pharmacol*, 34: 429 – 434.

Corneal permeability velocity and hydration rate (corneal swelling) of tetracaine and other ester local anesthetics was determined in the rabbit. Albino rabbit eyes were isolated and the sclera excised along the external margin 2-3 mm from the corneal outline and placed in the center of a corneal permeability experimental chamber. Samples of cocaine·HCL procaine·HCl and tetracaine·HCl were prepared at concentrations of 0.25, 0.5 and 1% dissolved in an artificial tear solution. This solution and artificial aqueous humor solution were placed into the tear side and aqueous humor side of the chamber, respectively. After specified incubation times, the volumes of solutions on both sides of the chamber were measured. In addition the amount of anesthetic on the aqueous humor side and the residual quantity on the tear side were also measured. For the determination of corneal hydration, the wet weight of only the corneal permeable area (7 mm in diameter) was determined immediately after excision from the sclerocorneal specimen and removal of surface water on the cornea after incubation.

Compared to cocaine and procaine, tetracaine demonstrated the lowest permeability and highest hydration rate. Permeability appeared to be a passive process and was indirectly proportional to molecule size when compared to other ester local anesthetics.

Melanin binding

Buszman, E., 2003, “Effect of metal ions on melanin—local anaesthetic drug complexes”, *Bioinorg Chem Appl*, 113 – 22.

The study examined the *in vitro* interaction of tetracaine and other ester anesthetics with melanin in the presence of metal ions. Based on the resultant association constants, the following order of drugs affinity to melanin was found: tetracaine > procaine >> bupivacaine > lidocaine. Tetracaine was shown to bind melanin at strong and weak binding sites with association constants (K_1 and K_2) of $3.61 \times 10^5 \text{ M}^{-1}$ and $4.43 \times 10^3 \text{ M}^{-1}$, respectively. The data also reveal that the presence of $\text{Cu}^{(2+)}$ and $\text{Zn}^{(2+)}$ ions incubated with melanin before complexing with the drugs decrease the total amount of anesthetic bound to melanin presumably through competition for binding sites. The authors suggest that blocking active centers in melanin molecules by metal ions, which potentially exist in living systems, may change the clinical therapeutic efficiency of the anesthetic drugs.

6 General Toxicology

6.1 Single-Dose Toxicity

The applicant cited data presented in Registry of toxic effects of chemical substances: Tetracaine, 2012:

Table 10. Acute toxicity of tetracaine hydrochloride

Species	Route	LD ₅₀ Dose
rat	intraperitoneal	33 mg/kg (198 mg/m ²)
	intrathecal	4 mg/kg (24 mg/m ²)
	intravenous	6 mg/kg (36 mg/m ²)
mouse	intraperitoneal	20 mg/kg (60 mg/m ²)
	intravenous	6 mg/kg (18 mg/m ²)
	oral	300 mg/kg (900 mg/m ²)
rabbit	intratracheal	6.5 mg/kg (366 mg/m ²)
	parenteral	33.5 mg/kg (402 mg/m ²)

7 Genetic Toxicology

In the labeling for Pliaglis, the following information is presented (statements regarding ^{(b) (4)} are omitted):

^{(b) (4)}

No other genetic toxicology studies were conducted or referenced by the Applicant.

8 Carcinogenicity

In the labeling for Pliaglis, the following statement is made:

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of either lidocaine or tetracaine.

No other carcinogenicity studies were conducted or referenced by the Applicant.

9 Reproductive and Developmental Toxicology

Fertility (b) (4)

Regarding fertility (b) (4), the Pliaglis labeling says the following regarding tetracaine (statements regarding lidocaine are omitted):

Tetracaine did not affect fertility in male or female rats when given as subcutaneous doses up to 7.5 mg/kg (equivalent to the level of tetracaine in the lowest approved dose of PLIAGLIS Cream on a mg/m² basis).

(b) (4)

10 Special Toxicology Studies

Patton, T. and J. Robinson, 1975, "Influence of topical anesthesia on tear dynamics and ocular drug bioavailability in albino rabbits", *J Pharm Sci*, 64: 267 – 271.

The bioavailability of topically applied tetracaine on tear production and instilled solution drainage was determined. Male albino rabbits received a drop of tetracaine (0.5%) in the test eye or a drop of normal saline in the contralateral eye as control. Determination of lacrimal turnover rate and instilled solution drainage rate was determined using a radioactive technetium tracer. Tear secretion was determined using Schirmer strips.

Tetracaine hydrochloride caused a significant, dose-dependent decrease in the normal turnover rate of the lacrimal fluid, indicating decreased tear production (Table 1). Tetracaine caused significant reductions in the tear production up to 70% as shown by secretion tests.

Table 11. Turnover rate of instilled volume of technetium (25 μL) in rabbits following various doses of tetracaine	
Number of drops instilled	Turnover rate (μ L/min)
0	0.66
1	0.20
2	0.19
3	0.13
4	0.11
5	0.10

Tetracaine hydrochloride caused a dose-dependent reduction in the drainage rate of an instilled solution.

Table 12. Drainage rate constants of lacrimal fluid in rabbits following various doses of tetracaine	
Number of drops instilled	Drainage rate (min^{-1})
0	0.54
1	0.39
2	0.35
3	0.42
4	0.12
5	0.06

Sarchahi, A. and H. Bozorgi, 2012, "Effect of tetracaine on intraocular pressure in normal and hypertensive rabbit eyes", *J Ophthalmic Vis Res*, 7: 29 – 33.

The study was conducted on 12 healthy rabbits as controls and 6 healthy rabbits in which an experimental model of ocular hypertension (OHT) was induced by administration of 70 mL/kg of tap water through an orogastric tube. One drop of tetracaine was instilled in the left eye while a drop of normal saline (placebo) was applied to the right eye with the instillation of drops repeated after 55 minutes. IOP was measured before and at specific times after drop administration.

Tetracaine treated eyes in both groups (ocular hypertensive and normal controls) demonstrated significant IOP reduction at time zero (immediately after drop instillation) which was sustained up to 20 minutes, as compared to placebo treated eyes ($P < 0.05$). In ocular hypertensive rabbits, repeat instillation of tetracaine at 55 minutes significantly reduced IOP immediately and up to 30 minutes thereafter.

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Boillot T, et al., 2013, "Effect of topical application of tetracaine on intraocular pressure in dogs: preliminary results", *J Fr Ophthalmol*, 36(5):402-7.

NOTE: Article available only in French, therefore only the English abstract is included, verbatim:

PURPOSE:

To evaluate the effect of topical application of tetracaine on intraocular pressure (IOP) measurement by Tonopen in dogs.

SUBJECTS AND METHODS:

Six healthy male Epagneul Bretons (group 1) and six healthy male black Labrador Retrievers (group 2) were examined. IOP was measured in the right eye (OD) prior to (IOP1) and 1 minute following instillation of one drop of topical tetracaine (IOP 2), and the left eye (OS) (control) prior to (IOP 3) and 1 minute following instillation of one drop of isotonic saline solution (IOP 4). Measurements were performed on two occasions: at 8:00 AM and 3:00 PM.

RESULTS:

For both groups, IOP measurements were higher in the morning than in the afternoon. For group 1, IOP1 mean (SD), IOP2 mean (SD), IOP3 mean (SD) and IOP4 mean (SD) were 14.6 (2.2) mmHg, 11.3 (3.2) mmHg, 14.4 (2.2) mmHg and 13.5 (3.9) mmHg respectively, while in group 2, IOP1 mean (SD), IOP2 mean (SD), IOP3 mean (SD) and IOP4 mean (SD) were 14.2 (3.8) mmHg, 9.5 (3.7) mmHg, 13.5 (2.8) mmHg and 13.0 (3.8) mmHg respectively. For both groups at each time

point, IOP 2 values were significantly lower ($P < 0.007$) than IOP 1 values, whereas IOP 3 and 4 values were not significantly different ($P > 0.27$).

CONCLUSION:

This study demonstrates that topical application of tetracaine significantly lowers IOP measured by Tonopen due to a possible interaction with melanin. The potential effect of topical anesthetics should be taken in consideration when performing applanation tonometry for clinical, pharmacological and toxicological studies.

11 Integrated Summary and Safety Evaluation

The NDA is approvable from a Pharmacology/Toxicology perspective. Publications submitted by the applicant establish systemic safety pharmacology at high systemic doses of tetracaine and some ocular effects including a temporary decrease in intraocular pressure and reduced tear production and turnover. No other ophthalmic toxicity has been reported.

As a 505(b)(2) NDA application, safety margins established for the listed drug, Pliaglis, and a long history of pre-approval topical ophthalmic use in the patient population indicated adequately characterize the safety profile of this formulation of tetracaine administered via topical ophthalmic drop.

Regarding product-related impurities and (b) (4), two impurities identified by the applicant are proposed at specifications which exceed those recommended in ICH Q3B(R2). (b) (4) are proposed at no more than (b) (4)% and (b) (4)%, respectively. There were no nonclinical data submitted to qualify these impurities above ICH recommended concentrations. The applicant stated that the formulation, manufacturing process, including key process parameters and controls for (b) (4) of blister packs for the proposed drug product are the same as those of the historically marketed commercial product, however, no historical data regarding content of the proposed impurities in previously marketed clinical batches was provided. An assessment of comparability of Tetracaine hydrochloride ophthalmic solution 0.5% to the historically marketed commercial product is deferred to the CMC team, and an assessment of the adequacy of the historic clinical data to support safety is deferred to the Clinical team.

The applicant has proposed drug product acceptance limits for (b) (4)

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

12 Appendices

APPENDIX A: Impurity QSAR analysis review (CDER/OTS/OCP/DARS)

(b) (4)
were evaluated by CDER/OTS/OCP/DARS for bacterial mutagenicity using (quantitative) structure-activity relationship [(Q)SAR] models. Three software programs were used: *Derek Nexus* 4.1.0 (*DX*), *Leadscope Model Applier* 2.0.3-1 (*LMA*), and *CASE Ultra* 1.5.2.0 (*CU*). To maximize sensitivity and negative predictivity, a positive prediction from any one software program was used to justify a positive overall prediction.

The (Q)SAR assessment of mutagenic potential is consistent with recommendations described in the ICH M7 guideline (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies). All (Q)SAR model outputs were reviewed with the use of expert knowledge in order to provide additional supportive evidence on the relevance of any positive, negative, conflicting or inconclusive prediction and provide a rationale to support the final conclusion.

A SAR analysis was also performed by the sponsor using the expert rule-based system *Derek Nexus* 4.1.0. No structural alerts were identified for bacterial mutation. The sponsor's (Q)SAR assessment uses only a single methodology, which is consistent with the ICH M7 guideline's implementation period recommendations. In order to confirm the results of *Derek Nexus* and to provide additional weight to the prediction, the test compounds were run against the software programs currently used for in-house consultations by the (b) (4). Based on the entire weight of evidence, the two degradants identified in NDA 208135 are predicted to be negative for bacterial mutagenicity.

(b) (4)

(b) (4) is predicted to be negative for bacterial mutagenicity. The *CU* equivocal prediction for *Salmonella* mutagenicity is based on the presence of alerting fragment (b) (4). The *LMA* equivocal prediction for *E.coli/TA102* mutagenicity is based on the presence of the scaffold (b) (4) substructure. A review of the training set structures behind both alerts revealed that many of the chemicals also possess known reactive groups likely responsible for their reactivity (e.g., (b) (4), (b) (4)). In addition, these fragments are found in the empirically negative API, tetracaine, thus can be discounted in accordance with the ICH M7 guideline.

<i>Salmonella</i>	<i>E.coli/TA102</i>
(b) (4)	

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/s/

AARON M RUHLAND
01/25/2016

LORI E KOTCH
01/25/2016

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208135

Applicant: Alcon Research Ltd **Stamp Date:** 4/30/2015

Drug Name: Tetracaine hydrochloride
ophthalmic solution 0.5% Steri-Unit®

NDA/BLA Type: Type 7 (drug
already marketed without
approved NDA)

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	✓		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	✓		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	✓		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?		✓	1) No nonclinical ocular toxicity studies were submitted or referenced 2) Applicant will rely on previous Pharmacology/Toxicology NDA (NDA 21-717; Pliaglis Lidocaine; Tetracaine 7%; 7% topical cream) for genotoxicity and reproductive toxicity assessment
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).		✓	The applicant will rely on extensive clinical experience with the study drug to support the ocular formulation and route of administration (to date the formulation has been marketed without NDA approval for 45 years by the applicant)
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?		✓	The applicant will rely on extensive human safety data for ocular safety
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?		✓	

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			-Not applicable
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57?		✓	Safety margins presented in the labeling not expressed as mg/m ² , rather they were calculated based on comparison of dose in mg/kg.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			Applicant states that impurities which exceed ICH Q3B limits are not relevant given single dose regimen. The acceptability of the specifications will be a review issue.
11	Has the applicant addressed any abuse potential issues in the submission?		✓	
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?		✓	

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

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/s/

AARON M RUHLAND
06/08/2015

LORI E KOTCH
06/08/2015