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RESEARCH**

APPLICATION NUMBER:

208135Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	208-135
Submission Date(s):	April 30, 2015
PUDFA:	February 29, 2016
Drug	Tetracaine hydrochloride
Product/Formulation; Strength(s)	Tetracaine Hydrochloride Ophthalmic Solution 0.5%
Primary Reviewer	Yongheng Zhang, Ph.D.
Team Leader	Philip Colangelo, Pharm D, Ph D
OCP Division	DCP4
OND Division	DTOP/OAP
Applicant	Alcon Research Ltd
Proposed indication	For procedures requiring a rapid and short-acting topical ophthalmic anesthetic
Dose and Administration	One drop topically in the eye(s) as needed
Submission Type	505(b)(2) ; Standard

SUMMARY

Tetracaine Hydrochloride Ophthalmic Solution 0.5% (STERI UNITS®) is a pre-sterilized ready-to-use topical anesthetic product for ocular use. It is a single-use product intended for procedures in which rapid and short-acting anesthesia is required such as in tonometry, gonioscopy, removal of corneal foreign bodies, conjunctival scraping for diagnostic purposes, suture removal from the cornea, other short corneal, and conjunctival procedures.

Tetracaine Hydrochloride has been marketed, without FDA's approval, as an ophthalmic solution from several manufactures in the United States for more than 45 years as a topical anesthetic in ophthalmologic procedures.

The current submission is a literature-based 505(b)(2) application. The applicant has not conducted any additional clinical studies to support the NDA.

The sponsor did not conduct any clinical pharmacology related studies and requested the waiver of evidence of in vivo bioavailability or bioequivalence. In accordance with the 21 CFR §320.22(e) (see below), the reviewer grants the waiver of evidence of in vivo bioavailability or bioequivalence to this NDA on the basis of the compatibility with the protection of public health due to its long history of clinical use.

21 CFR §320.22(e)

FDA, for good cause, may waive a requirement for the submission of evidence of in vivo bioavailability or bioequivalence if waiver is compatible with the protection of the public health.....

RECOMMENDATIONS

The Clinical Pharmacology information provided by the Applicant in the NDA is acceptable and the reviewer recommends approval of Tetracaine Hydrochloride Ophthalmic Solution 0.5%.

The reviewer's proposed label changes in Appendix 1 should be forwarded to the sponsor.

Appendix 1. Proposed Labeling with Revisions

The following proposed labeling has been marked with revisions made by the Clinical Pharmacology Reviewer.

(Underline = Clin Pharm reviewer's addition; strikethrough = Clin Pharm reviewer's deletion)

12. CLINICAL PHARMACOLOGY

12.3. Pharmacokinetics

The systemic exposure to tetracaine following topical administration of Tetracaine Hydrochloride Ophthalmic Solution 0.5% has not been studied. Tetracaine hydrochloride is (b) (4) metabolized by plasma pseudocholesterases and nonspecific esterases in ocular tissues (b) (4).

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/s/

YONGHENG ZHANG
10/13/2015

PHILIP M COLANGELO
10/13/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208135	SDN	001
Applicant	Alcon Research Ltd	Submission Date	04/30/2015
Generic Name	Tetracaine Hydrochloride	Brand Name	
Drug Class	Ester-linked local anesthetic		
Indication	For procedures requiring a rapid and short-acting topical ophthalmic anesthetic		
Dosage Regimen	instill 1 drop in the eye(s) as needed		
Dosage Form	Ophthalmic solution	Route of Administration	Topical ocular
OCP Division	IV	OND Division	DTOP
OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader	
Division	Yongheng Zhang, Ph.D.	Philip Colangelo Pharm. D., Ph.D.	
Pharmacometrics	-		
Genomics	-		
Review Classification	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Expedited		
Filing Date	6/29/2015	74-Day Letter Date	7/13/2015
Review Due Date	1/25/2016	PDUFA Goal Date	2/29/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

- Yes
 No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

- Yes
 No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

- Yes
 No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	Clinical Pharmacology Summary	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Bioanalytical and Analytical Methods	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	Labeling	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
<input checked="" type="checkbox"/> Metabolism Characterization	3	Literature data only
<input type="checkbox"/> Transporter Characterization		
<input type="checkbox"/> Distribution		
<input type="checkbox"/> Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		

<input type="checkbox"/> Absolute Bioavailability			
<input checked="" type="checkbox"/> Relative Bioavailability	5	Literature data only– See Notes below	
<input type="checkbox"/> Bioequivalence			
<input type="checkbox"/> Food Effect			
<input type="checkbox"/> Other			
Human Pharmacokinetics			
Healthy Subjects	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
Patients	<input type="checkbox"/> Single Dose		
	<input type="checkbox"/> Multiple Dose		
<input type="checkbox"/> Mass Balance Study			
<input type="checkbox"/> Other (e.g. dose proportionality)			
Intrinsic Factors			
<input type="checkbox"/> Race			
<input type="checkbox"/> Sex			
<input type="checkbox"/> Geriatrics			
<input type="checkbox"/> Pediatrics			
<input type="checkbox"/> Hepatic Impairment			
<input type="checkbox"/> Renal Impairment			
<input type="checkbox"/> Genetics			
Extrinsic Factors			
<input type="checkbox"/> Effects on Primary Drug			
<input type="checkbox"/> Effects of Primary Drug			
Pharmacodynamics			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
Pharmacokinetics/Pharmacodynamics			
<input type="checkbox"/> Healthy Subjects			
<input type="checkbox"/> Patients			
<input type="checkbox"/> QT			
Pharmacometrics			
<input type="checkbox"/> Population Pharmacokinetics			
<input type="checkbox"/> Exposure-Efficacy			
<input type="checkbox"/> Exposure-Safety			
Total Number of Studies		In Vitro	In Vivo
Total Number of Studies to be Reviewed			

Criteria for Refusal to File (RTF)		
RTF Parameter	Assessment	Comments
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	In vivo bioavailability waiver request submit
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
Complete Application 10. Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> N/A	

Notes:

This NDA is a literature-based 505(b)(2) application. The sponsor submitted a list of published clinical pharmacology studies (*see below*) of tetracaine following either dermal or intranasal administration. These data may have limited relevance to the systemic exposure of tetracaine following topical ocular administration of the ophthalmic solution.

Study Design	Study Objectives	No. of Patients	Dosing Regimen	Reference
Double masked	To compare the percutaneous absorption of tetracaine and seven other anesthetics	15	0.5 g of anesthetic to ventral surface of forearm for 30 min	McCafferty 1988
Nonrandomized, controlled (fellow eye)	To determine corneal epithelial permeability after instillation of anesthetics and preservatives	10–12	50 µL of 1% tetracaine every 2 min × 5	Ramselaar 1988
Non-controlled	To assess safety and absorption of tetracaine cream	10	Topical application of tetracaine cream 2 g (5% w/w) for 240 min	Mazumdar 1991
Nonrandomized, controlled trial over a 5-month period	To measure plasma cocaine and tetracaine levels in children after standardized application of a solution of tetracaine 0.5%, epinephrine 0.05%, and cocaine 11.8% (TAC) to lacerations requiring suture repair	77	3 mL TAC for 15 min	Terndrup 1992
Randomized, factorial design	To measure and evaluate the detectable plasma levels and safety of lidocaine and tetracaine (LT) in adult volunteers after a single application of an LT peel	36	7% tetracaine/7% lidocaine peel applied 50, 100, or 200 cm ² for 30, 60, or 90 min	Ogden 2008
Non-controlled	To measure the cardiovascular effects and pharmacokinetics of intranasal tetracaine plus oxymetazoline	12	18 mg tetracaine/0.3 mg oxymetazoline once or twice	Giannakopoulos 2012

From 2.7.2 Summary of Clinical Pharmacology Studies.

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/s/

YONGHENG ZHANG
06/23/2015

PHILIP M COLANGELO
06/23/2015