CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211039Orig1s000

SUMMARY REVIEW

Deputy Division Director Review,
Cross-Discipline Team Leader Review, and Clinical Review
of NDA 211039 Class 2 Resubmisson

Date	3/9/20
From	Wiley A. Chambers, M.D., William M. Boyd, M.D., Lucious Lim, M.D.
Subject	Division Director Review, Cross-Discipline Team Leader Review, and Clinical Review
NDA#	NDA 211039
Applicant	Bausch Health Ireland Limited
Date of Class 2 Resubmission	December 16, 2019
PDUFA Goal Date	June 16, 2020
Proprietary Name	Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution, 0.3%/0.4%
Established Name	fluorescein sodium and benoxinate hydrochloride ophthalmic solution, 0.3%/0.4%
Dosage Form	Topical ophthalmic solution
Indication	For ophthalmic procedures requiring a disclosing agent in combination with a topical anesthetic
Dosing Regimen	Instill 1 to 2 drops in eye prior to ophthalmic procedure
Regulatory Action	Approval

1. Introduction/Benefit-Risk Assessment

Fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% is a combination product that contains fluorescein, a disclosing agent, and benoxinate, a topical anesthetic. This combination is beneficial for use in corneal and conjunctival eye procedures.

The drug product that is the subject of this NDA is the same drug product and formulation as has been marketed by Bausch & Lomb since 1994 as an unapproved drug product. The formulation was developed in 1993 as a direct copy of Fluress Ophthalmic Solution, which was commercially available at the time as an unapproved new drug product. It is a sterile, preserved (chlorobutanol 1%), ophthalmic solution presented in a 6 cc amber glass bottle with a 20mm polypropylene black cap with a (b) (4). A sterile dropper is included for administration of the drug product to the eye, by a physician. Once the bottle is opened the dropper will replace the 20mm polypropylene cap until the product is discarded.

This is a 505(b)(2) application based on literature reports provided by a literature review conducted by the applicant and by an additional literature review conducted by the Medical Officer. The reference listed product on the applicant's 356h Form is AltaFluor Benox NDA 208582. NDA 208582 was also a 505b)(2) application which also relied on published literature to establish safety and efficay.

This is a Class 2 Resubmssion. The application received a Complete Response letter on July 19, 2019. Per the letter:

> We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. Specifically, the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance do not comply with the current good manufacturing practice regulations in parts 210 and 211. During a recent inspection of (b) (4) manufacturing facility, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved and all facilities used for the manufacture, processing, packing, or holding of the drug substance and drug product will need to be in compliance with the current good manufacturing practice regulations in parts 210 and 211.

The letter also contained comments/recommendations that were not approvability issues.

Benefit-Risk Assessment Framework

The literature studies demonstrate that this combination allows clinicians to perform corneal and conjunctival eye procedures which would otherwise not be able to be performed. Fluorescein sodium is a dye and is the gold standard diagnostic tool for determining breaks in the corneal epithelium. The purpose of the anesthetic, benoxinate hydrochloride, in this combination product is to permit contact with the ocular surface to reduce discomfort from the ophthalmic procedure.

The adverse event profile for fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% based on the published studies and post-marketing reporting of marketed, unapproved products suggest that the most common adverse events are bulbar conjunctival erythema, burning, coldness, corneal desquamation, corneal staining, discomfort, dizziness, dull ache, fainting, irritation, mild conjunctival infection and punctate keratitis. Some of which is due to the diagnostic procedure being performed or to the underlying condition.

The benefits of using this drug product outweigh the risks for the intended indication.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Certain corneal and conjunctival procedures require that a disclosing agent be used to perform the procedure. A topical anesthetic is needed to allow close contact with the cornea. For example, applanation tonometry to measure intraocular pressure (IOP) is a commonly performed ocular procedure that requires a disclosing agent and a topical anesthetic.	Applanation tonometry was able to be performed after applying fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4%
Current Treatment Options	• The individual components are available and one other combination of these same two agents (different formulation) is approved for the same use.	This product will provide an alternative to the one approved fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.25%/0.4% combination product.
Benefit	• Ocular procedures can be performed following application of fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4%.	The procedures were successfully performed.
Risk and Risk Management	• Use of the anesthetic produces a temporary risk to ocular injury due to a temporary loss of the corneal reflex.	Patients can be warned to take care to avoid ocular injury during the period in which there is a loss of corneal reflex.

2. Background

Fluorescein Sodium and Benoxinate Hydrochloride have been used together as a combination product for many years, and has been commercially available since 1966. Until recently all formulations of the product were marketed without FDA approval. In December 2017, Altaire Pharmaceuticals Inc. received FDA approval to market Altafluor Benox (NDA 208582), a combination drug product containing fluorescein sodium 0.25% and benoxinate hydrochloride 0.4%.

Fluorescein is also marketed as an injectable to be administered intravenously (IV). The IV form of fluorescein is marketed as the Alcon product [NDA 21-980, Fluorescite (fluorescein injection, USP) 10%] which was approved in 2006, the Akorn products [NDA 22-186 AK-Fluor (fluorescein injection, USP) 10% and 25%] and the withdrawn Novartis product [NDA 17-869]. The injectable product is indicated in diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature.

Benoxinate hydrochloride is a topical anesthetic. Benoxinate hydrochloride ophthalmic solution, 0.4%, was originally permitted in 1953 as Dorsacaine under NDA 08-729. The product was reviewed as part of the Drug Efficacy Study Implementation (DESI) and found to be effective.

3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Sec 8Clinical
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	

		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

4. Product Quality

From the Product Quality review dated March 4, 2020:

The product, as historically marketed by the applicant, was labeled as Fluorescein Sodium 0.25% and Benoxinate Hydrochloride 0.4% Ophthalmic Solution and contains [redacted] in order to [redacted] support the safety and efficacy of the product.

Composition of Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution 0.3%/0.4%

Component	Formulation Quantity	Function	Quality Standard
Fluorescein Sodium[1]	[redacted]	Active Ingredient	USP
Benoxinate hydrochloride[1]	0.4%[3]	Active Ingredient	USP
Chlorobutanol	[redacted]	Antimicobial Preservative	NF
Boric Acid	[redacted]	[redacted]	NF
Povidone	[redacted]	[redacted]	USP
Hydrochloric Acid	[redacted]	pH Adjustment	NF
Water for injection (WFI)	[redacted]	[redacted]	USP
[redacted] nited States Pharmacopeia Q.S.=Quantity Sufficient			

Source: Module 3.2.P.1. Description and Composition of the Drug Product

[redacted] that the product contains fluorescein sodium 2.6 mg/mL (0.3%) and benoxinate hydrochloride 4.4 mg/mL (0.4%).

Container Closure System

Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution, 0.3% /0.4% is supplied as a 5 ml fill contained in a 6 cc amber glass bottle, with a 20 mm Polypropylene screw cap.

Primary Container Closure System

Components		Description	DMF Number
Bottle	Size	6 cc	[redacted]
	Description	Amber Glass Vial	
	Manufacturer	[redacted]	
	Glass Type	Type [redacted]	
	Colorant	N/A	
	Cross-Reference to Drawing	6 cc Bottle Drawing	
Closure	Size	20mm	
	Description	Polypropylene, Black Cap [redacted]	
	Manufacturer	[redacted]	
	Cross-Reference to Drawing	C20/400 Cap Drawing	

Source: Module 3.2.P.7. Container Closure System

Release and shelf life specifications for Fluorescein Sodium (b) (4) % and Benoxinate Hydrochloride 0.4% Ophthalmic Solution

Test	Procedure	Acceptance Criteria	
		Release	Stability
Description	Visual	Clear, orange-colored solution	
Identification A: Fluorescein Sodium	Current USP	Positive for Fluorescein Sodium. The fluorescence disappears when the solution is made acidic and reappears when the solution is again made alkaline.	Not tested on stability
(b) (4)			
Identification B: Benoxinate Hydrochloride		PDA Spectrum: The spectrum for Benoxinate corresponds to that of the standard.	Not tested on stability
Assay: Fluorescein Sodium	23-T301	90.0 – 120.0% of label	
Assay: Benoxinate Hydrochloride		90.0 – 120.0% of label	
Chromatographic Impurities	23-T301	Specified Identified Impurity: (b) (4)	NMT (b) (4) %

Test	Procedure	Acceptance Criteria	
		Release	**Stability**
		Specified Identified Impurity: [redacted]	NMT [redacted]%
		Specified Unidentified Impurity [redacted]	NMT [redacted]%
		Specified Unidentified Impurity [redacted]	NMT [redacted]%
		Any Other Unspecified Impurity	NMT [redacted]%
Total Impurities	23-T301	Release NMT [redacted]%	Stability NMT [redacted]%
Assay: Chlorobutanol[1]	23-T302	[redacted]% of label	
pH	Current USP	4.3 – 5.3	
Osmolality	Current USP	Release 316 - 348 mOsm/kg	Stability 297 – 385 mOsm/kg
Particulate Matter	Current USP <788>	NMT 6000 particles per container ≥ 10 µm and NMT 600 particles per container ≥ 25 µm	
Antimicrobial Effectiveness Testing	Current USP	Not tested	Meets USP requirements
Sterility	Current USP	Meets USP requirements	

1: Antimicrobial effectiveness (AE) confirmatory testing may be performed at any interval if the corresponding chlorobutanol content does not meet the lower limit of the acceptance criterion. If the chlorobutanol chemical results are out-of-specification, an AE challenge will be performed. Below specification chlorobutanol content is not a basis for failure if the antimicrobial effectiveness requirement is met

2: Relative retention time (RRT) for specified impurities are typically ± [redacted].

USP: United States Pharmacopeia
NMT: Not More Than
mOsm: Milliosmoles
kg: Kilogram
mL: Milliliter
NLT: Not Less Than

Source: Module 3.2.P.5.1 Specifications

From the Product Quality review dated 3/4/20:

Facilities Inspections

An overall acceptable cGMP recommendation for all of the facilities was issued on 2/27/20.

Summary of Drug Substance Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
(b) (4)			Medium risk	Acceptable, based on profile
			Low risk	Also the DP manufacturer. See below for the recommendation.
			High risk	Acceptable, based on follow-up on PAI inspection
			High risk	Acceptable, based on profile
			High risk	Acceptable, based on profile

Summary of Drug Product Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
[redacted] (b) (4)			High risk	PAI Inspection conducted. A post-approval inspection is recommended
Bausch & Lomb, Inc.	1317628	Drug product analytical and microbiological release and stability testing (CTL)	Medium risk	Acceptable, based on profile.
[redacted] (b) (4)			Medium risk	No further evaluation

Product Quality Recommendations and Conclusion on Approvability

NDA 211039 is recommended for approval from a Product Quality perspective.

The applicant concurred with the following two OPQ post marketing commitments on Mar 4, 2020:

1. Post Marketing Commitment# 3817-1[1]: Provide the compatibility study reports of the bulk solution statically contacting with each (b) (4) component (b) (4) [redacted] for 24 hours. Establish a control strategy (b) (4) to mitigate the risks from the incompatibility of the (b) (4) components (b) (4) [redacted].

[1] An administrative error occurred when the PMC entry into the archival system was duplicated; this resulted in new PMC numbers being generated and replaced the previous record. The two PMC tracking numbers, 3817-1 and 3817-2, in this review and in the action letter are correct.

Final protocol submission date: May 15, 2020; study completion: August 15, 2020; and final report submission: October 15, 2020.

2. Post Marketing Commitment# 3817-2: Establish a procedure which ensures that bulk solution (b) (4) nd update the master batch record accordingly.

Final protocol submission date: May 15, 2020; study completion: August 15, 2020; and final report submission: October 15, 2020.

5. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology review dated 7/3/2019:

No original nonclinical studies were submitted to support the safety of the combination. The nonclinical support is based on published literature for each individual active component. Given the extensive clinical experience with both fluorescein sodium 0.25% and benoxinate hydrochloride 0.4% used individually or in combination at the intended dose regimen, and the use of common ocular excipients in the clinical formulation, there are no specific nonclinical concerns regarding the approval of this NDA.

6. Clinical Pharmacology

No new clinical pharmacology or clinical studies were performed or were included in this NDA submission.

Maximal corneal anesthesia usually occurs in about 5-45 seconds and lasts about 20 minutes after single administration. The anesthetic effect may be extended by subsequent administration 10-20 minutes after the last administration.

7. Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

8. Clinical/Statistical- Efficacy

From the Clinical review dated 7/15/2019:

No new clinical trials were conducted by the applicant to assess the safety and/or efficacy of fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4%. This is a 505(b)(2) application based on literature reports provided by a literature review conducted by the applicant and by an additional literature review conducted by the Medical Officer.

The product, as historically marketed by the applicant, was labeled as Fluorescein Sodium 0.25% and Benoxinate Hydrochloride 0.4% Ophthalmic Solution (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) the product contains fluorescein sodium 2.6 mg/mL (0.3%) and benoxinate hydrochloride 4.4 mg/mL (0.4%).

The study objectives of many of the submitted literature references were different than those of interest in this application. In this review, references are evaluated to determine if evidence of the proposed drug product's effectiveness to provide adequate fluorescence and topical anesthesia in order that IOP measurement or other ophthalmic procedures could be performed was demonstrated.

The evaluation of the drug product for the intended indication begins with the acknowledgement that it is self-evident that a topical anesthetic is required to perform any ophthalmic procedure on a conscious patient. Thus, the literature reports submitted support the efficacy of fluorescein sodium and benoxinate hydrochloride (0.3%/0.4%) for the intended indication in that the following are present in each report:

- Fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% was administered.
- Fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% allowed applanation tonometry or other short corneal or conjunctival procedures to be successfully performed.
- Fluorescein sodium was necessary and the concentration sufficient to perform Goldmann applanation tonometry and/or visualize the corneal epithelium successfully and accurately.
- Benoxinate sodium 0.4% provided adequate anesthesia to perform Goldmann applanation tonometry, or other short corneal or conjunctival procedures successfully and accurately.

Seven literature reports of controlled, prospective studies evaluating fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% in providing visualization and topical anesthesia form the primary basis of support for efficacy. An additional five literature reports of controlled, prospective studies evaluating fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.25%/0.4% in providing adequate visualization and topical anesthesia in pediatric patients form the primary basis of support for efficacy in the pediatric population.

Table 8.1 Key Clinical Efficacy Studies Submitted from Published Literature

Reference	Subject Objective	Study Design Study Setting	No. of Patients/ Patient Demographics	Fluorescein and Benoxinate Ophthalmic Solution Information Manufacturer	Comments/ Findings
Efficacy of Fluorescein Sodium 0.3% and Benoxinate Hydrochloride 0.4% for Applanation Tonometry					
Hales 1967	Assess IOP (by GAT) using a sterile Benoxinate and Fluorescein Ophthalmic Solution	Retrospective, non-randomized, unmasked Provo, UT	N=1381 M/F: 644/737 Age range: 5-96 yrs (No. of pediatric patients NR)	Fluress (fluorescein 0.3%- benoxinate 0.4%) Barnes-Hind Labs [a, b]	DP provided adequate anesthesia and dye patterns for GAT
Quickert 1967	Assess effectiveness and tolerability of 2 fluorescein-anesthetic solutions	Double-blind crossover trial Dept. of Ophthalmology UCSF, San Francisco, CA	N=50; 100 eyes underwent IOP assessment using 2 different fluorescein-anesthetic solutions	Fluress (fluorescein 0.3%- benoxinate 0.4%); 0.5% proparacaine and 0.3% fluorescein ophth. soln. Manufacturer not specified. [b]	Benoxinate 0.4% and fluorescein 0.3% ophth. soln appeared to be similarly effective.
Katz et al. 1976	Compare IOP-lowering effect of timolol to that of placebo in healthy volunteers	Double-blind RCT. Patients assigned to timolol or placebo. IOP was assessed by GAT at 6 time points on Days 1, 8, and 15.	N=30 Ages 20-48 yrs	Fluress (fluorescein 0.3%- benoxinate 0.4%) Manufacturer not specified. [b]	Some patients (n=NR) experienced bulbar conjunctival erythema or punctate keratitis.
Bright et al. 1981	Compare IOP assessed by GAT with or without fluorescein	Randomized, unmasked, crossover; matched-pairs analysis on 1 randomly selected eye from each patient Southern California College of Optometry, Fullerton, CA	N=100 200 eyes assessed with and without fluorescein	Fluress (fluorescein 0.3%- benoxinate 0.4%); Ophthetic (proparacaine HCl) 0.5% only Manufacturer not specified	• The correlation between IOP readings with and without fluorescein was significant (r=0.0552, p<0.01) • GAT w/o fluorescein underestimated IOP more in eyes with higher IOP. Safety and tolerability not reported.
Jose et al. 1983	Compare IOP assessed by GAT using benoxinate-fluorescein ophthalmic solution to that assessed by GAT using 0.5% proparacaine and fluorescein strip	Randomized, unmasked, crossover; first eye assessed selected randomly by coin flip School of Optometry, University of CA, Berkeley	N=14; 28 eyes underwent IOP assessment Gender, Age: NR	Fluress (fluorescein 0.3%- benoxinate 0.4%); Proparacaine 0.5% ophth. soln. with fluorescein strip Manufacturer not specified. [b]	• IOP assessed using fluorescein-benoxinate was significantly lower than that assessed using proparacaine-fluorescein strip. The difference was not considered clinically meaningful. Safety and tolerability not reported.

Reference	Subject Objective	Study Design Study Setting	No. of Patients/ Patient Demographics	Fluorescein and Benoxinate Ophthalmic Solution Information Manufacturer	Comments/ Findings
Ng et al. 2006	Compare the safety, validity, and comfort of benoxinate 0.4% and 0.35% fluorexon disodium to that of benoxinate 0.4% and 0.3% fluorescein ophthalmic soln.	Double-masked, randomized, crossover Southern CA college of Optometry, Fullerton, CA	N= 67; 134 eyes underwent IOP assessment with each comparator M/F: 35/32 Age: NR	AccuFluoro (fluorescein 0.3%-benoxinate 0.4%) FluraSafe (0.35% fluorexon-benoxinate 0.4%) Altaire Pharmaceuticals [c]	Fluorescein and fluorexon appear to be equally effective.
Other Uses of Fluorescein Sodium 0.3% and Benoxinate Hydrochloride 0.4%					
Khater et. al 2014	Role of argon laser as adjunctive therapy for corneal ulcers	Prospective, non-randomized, unmasked 1) local and systemic specific antimicrobial drugs + argon laser 2) Control=local and systemic specific antimicrobial drugs Tanta University, Tanta, Egypt	N=20	Manufacturer not specified	All patients treated with laser showed complete healing of epithelial defect within 4 weeks of laser treatment. In control group, 4 cases needed amniotic graft and other 6 cases healed from 3-7 weeks.

(b) (4)

Table 8.2 Key Clinical Efficacy Studies in Pediatric Patients Submitted from Published Literature

Reference	Subject Objective	Study Design Study Setting	No. of Patients/ Patient Demographics	Fluorescein and Benoxinate Ophthalmic Solution Information Manufacturer	Comments/ Findings
Yolton et al. 1980	Assess adverse events associated with ophthalmic diagnostic drugs in clinical setting	Cross-sectional study N=NR [d]; study tracked applications of drug rather than patient numbers; study evaluated more than 15,000 applications of various drugs, including 2,323 applications of fluorescein-benoxinate solution	N=247 Age 0-20 yrs: 236 Age 0-10 yrs: 11	Fluress (fluorescein sodium and benoxinate HCl, USP) 0.3%/0.4%; Proparacaine 0.5%; Tropicamide 0.5% and1.0%; Cyclopentolate 0.5 and1.0%; Phenylephrine 2.5%; and 10% ; Fluorescein;	Fluress applications recorded: 2323 total Age 0-10: 11 Age 11-20: 225 Age 21-30: 788 Age 31-40: 417 Age 41-50: 483 Age 51-60: 284 Age >60: 101 Age not spec.: 14

Reference	Subject Objective	Study Design Study Setting	No. of Patients/ Patient Demographics	Fluorescein and Benoxinate Ophthalmic Solution Information Manufacturer	Comments/ Findings
		Pacific University College of Optometry, Forest Grove, OR Feb. 1979 – April 1979		Rose Bengal Manufacturer not specified	
Qureshi 1997	Assess association between gender and IOP in subjects of different age groups	Cross-sectional study Rawalpindi Medical College, Rawalpindi, Pakistan	N= 7965 (15390 eyes) healthy subjects underwent assessment of IOP M/F: 5307/2388 Age ≥ 11 yrs Adult/Ped: 6152/ 1543 (age 11-20)	Fluress (fluorescein sodium and benoxinate HCl, USP) 0.3%/0.4% Manufacturer not specified [b]	Safety and tolerability not reported.
Eisenberg et al. 1998	Compare IOP assessed by GAT with IOP assessed by pneumotonometry	Non-randomized, unmasked, crossover, IOP was assessed by GAT first, followed by pneumotonometry; if data from both eyes of a patient were available, the average was reported New England Eye Center, Tufts Univ. School of Medicine, Boston, MA Nov. 1995 and July 1996	N= 72 GAT with Fluress N=33 pts presenting to the Pediatric Ophth. And Strabismus service Mean age: 14.5 Range (0-50 yrs) Adult/Ped: 4/29 Age 0-10 yrs: 7 Age 11-20 yrs: 12	Fluress (fluorescein sodium and benoxinate HCl, USP) 0.3%/0.4% Akorn, Inc.[a]	None
Bradfield et al. 2012	Assess agreement of IOP measured with Tono-Pen and GAT in normal children/ adolescents	Randomized, masked study Dept. of Ophthal and Visual Sciences, Univ. of WI, Madison	N= 439 (878 eyes) children/ adolescents (age 0-<18) underwent IOP	fluorescein combined with a topical anesthetic" No manufacturer information	None
Dosunmu et al. 2014b	Effect of body position on IOP	Prospective, randomized, unmasked Icare PRO vs Tono-Pen Duke University Eye Center Durham, NC	N=47 (94 eyes) Age: 8-17 (mean 12.7)	fluorescein sodium 0.3% and benoxinate HCl 0.4% Manufacturer not specified	Icare tonometer correlated well with GAT in the sitting position and with the Ton-Pen in both sitting and supine positions. IOP rises when a child changes position from sitting to supine, however the increase was < 1 mmHg.

(b) (4)

Summary Efficacy Statement

The literature studies contained in this submission support the efficacy of fluorescein sodium and benoxinate hydrochloride ophthalmic solution, 0.3%/0.4% for use in ophthalmic procedures requiring a disclosing agent in combination with an anesthetic.

The overall age range of patients from the key efficacy studies (Tables 8.1 and 8.2) was 0-96 years. Neonates were evaluated for safety and efficacy. No clinically relevant differences were observed based on demographic characteristics (i.e., age, race, sex) in the submitted literature reports.

Regarding fluorescein sodium ophthalmic solution, concentrations ranging from 0% to 0.5% were tested in four different literature reports. The 0.125% - 0.5% solutions were usable.

Regarding benoxinate hydrochloride ophthalmic solution, concentrations ranging from 0.1% to 0.5% were tested in four different literature reports. All concentrations provided adequate anesthesia for tonometry.

The safety and effectiveness of Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution, 0.3% /0.4% have been established for pediatric patients. Use of this drug product is supported by evidence from adequate and well controlled studies.

9. Safety

From the Clinical review dated 7/15/2019:

No clinical trials were conducted by the applicant to specifically address the safety of fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% as a disclosing agent and topical anesthetic for ophthalmic procedures; therefore, the safety of the product is based on the published literature and post-marketing reports.

Given its episodic and short term use, there are no published trials which evaluated its long term continuous use. Exposure to fluorescein and benoxinate ophthalmic solution (0.3%/0.4%) ranged from one dose per study eye to eight doses per study eye in one day. In studies in which dosing of the product occurred at multiple visits, the number of visit days ranged from 2 to 7 days over a period of 2 days to 12 months.

Reporting of adverse reactions attributable to the use of fluorescein sodium and benoxinate hydrochloride ophthalmic solution, 0.3%/0.4% was rare in clinical studies. The adverse reactions reported in these studies with the use of fluorescein sodium and benoxinate hydrochloride ophthalmic solution, 0.3%/0.4% were: bulbar conjunctival erythema, burning, coldness, corneal desquamation, corneal staining, discomfort, dizziness, dull ache, fainting, irritation, mild conjunctival infection and punctate keratitis.

Bausch Health submitted post-market experience data for the proposed drug product, fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4%. The applicant has been supplying fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% with the same formulation as the proposed drug product in the U.S. since 1994. The post-market safety data include spontaneous reports and reports in the published literature with a cutoff date of July 31, 2018.

Distribution Data Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution

YEAR	UNIT DISTRIBUTED
2009	469,498
2010	424,449
2011	383,355
2012	391,372
2013	562,752
2014	675,798
2015	443,617
2016	376,376
2017	8,554
Total	**3,735,771**

Post-Market Adverse Events Reported by ≥ 1 % From 1997 to July 31, 2018

Preferred Term	% of Total Reports	Total Number of Reports	Spontaneous Reports	Published Literature Reports
OCULAR				
Corneal abrasion	2.8%	8	7	1
Corneal disorder	1.3%	4	3	1
Eye irritation	2.2%	7	3	4
Eye pain	2.8%	9	8	1
Eye pruritus	1.3%	4	3	1
Keratitis	34.5%	109	27	82
Mydriasis	2.8%	9	9	0
Ocular hyperemia	1.3%	4	2	2
Vision blurred	1.3%	4	4	0
NON-OCULAR				
Dizziness	3.2%	10	10	0
Drug hypersensitivity	3.5%	11	11	0
Drug ineffective	1.3%	4	3	1
Nausea	3.2%	10	10	0
Seizure	1.3%	4	4	0
Vomiting	1.6%	5	5	0
TOTAL Patients in Database		**197**	**106**	**91**
TOTAL AEs in Database		**316**	**221**	**95**

The most common post-market ocular adverse events were keratitis (35%), corneal abrasion (3%), eye pain (3%), and mydriasis (3%). The most common non-ocular adverse events were drug hypersensitivity (4%), dizziness (3%), and nausea (3%).

Safety Update Report

A safety update is required upon resubmission of the NDA. Since the original NDA was submitted based on published literature and there have been no additional studies conducted by the applicant, this safety update is based on a literature search since the original submission date.

A search of PubMed, Google Scholar and Toxnet using the terms “fluorescein”, “benoxinate”, “oxybuprocaine”, “ocular”, “ophthalmic” and “eye” revealed the following published reports. A review of these reports reveals no new information that is considered by the applicant to affect the safety or labeling of Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution, 0.3%/0.4% for its intended use.

Summary Safety Statement

The adverse event profile for fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% based on the published studies and post-marketing reporting of marketed, unapproved products suggest that the most common adverse events are bulbar conjunctival erythema, burning, coldness, corneal desquamation, corneal staining, discomfort, dizziness, dull ache, fainting, irritation, mild conjunctival infection and punctate keratitis.

10. Advisory Committee Meeting

No Advisory Committee Meeting was held for this application. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

11. Pediatrics

The safety and effectiveness of Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution, 0.3%/0.4% have been established for pediatric patients. Use of Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution, 0.3%/0.4% is supported in pediatric patients by evidence from adequate and well controlled studies (see Section 8 of this review).

This application did not trigger PREA and was not presented at the Pediatric Review Committee (PeRC).

12. Other Relevant Regulatory Issues

BIOSTATISTICS

The published studies submitted in this NDA use the combination product or its individual components as an active control to evaluate the effectiveness of other products. The statistical team defered the filability and review to the clinical review team.

DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA)
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the submitted original draft labeling on 12/14/2018. There are no proposed labeling revisions in this review cycle other than minor editorial revisions.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)
The Office of Prescription Drug Promotion (OPDP) completed a formal review of the original package insert and labeling on 7/9/2019. There are no proposed labeling revisions in this review cycle other than minor editorial revisions.

FINANCIAL DISCLOSURE
This is a 505(b)(2) new drug application primarily based on literature. In accordance with 21 CFR Part 54, no financial disclosure is appropriate for this application. There are no "covered clinical studies" in this submission.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)
An Office of Scientific Investigations (OSI) audit was not requested. This is a 505(b)(2) supplemental application primarily based on literature.

13. Postmarketing Recommendations

NDA 211039 Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution, 0.3% /0.4% will be approved for procedures in adult and pediatric patients requiring a disclosing agent in combination with a topical ophthalmic anesthetic. There are no recommended postmarketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

14. Postmarketing Committments

The applicant concurred with the following two OPQ postmarketing commitments on Mar 4, 2020. The following comments will be conveyed to the applicant in the Approval regulatory action letter:

1. Post Marketing Commitment# 3817-1: Provide the compatibility study reports of the bulk solution statically contacting with each (b) (4) component (b) (4) for 24 hours. Establish a control strategy (b) (4) to mitigate the risks from the incompatibility of the (b) (4) components.

Final protocol submission date: May 15, 2020; study completion: August 15, 2020; and final report submission: October 15, 2020.

2. Post Marketing Commitment# 3817-2: Establish a procedure which ensures that bulk solution (b) (4) and update the master batch record accordingly.

Final protocol submission date: May 15, 2020; study completion: August 15, 2020; and final report submission: October 15, 2020.

15. Labeling

Attached at the end of this review is revised labeling submitted December 16, 2019, which is considered acceptable. There are no proposed labeling revisions in this review cycle other than minor editorial revisions.

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

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
03/09/2020 03:29:13 PM

WILEY A CHAMBERS
03/09/2020 03:31:59 PM