CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211039Orig1s000

CLINICAL REVIEW(S)

Deputy Division Director
and Cross-Discipline Team Leader Review of NDA 211039

Date	7/18/2019
From	Wiley A. Chambers, M.D. and William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review and Division Director Review
NDA#	NDA 211039
Applicant	Bausch Health Ireland Limited
Date of Submission	9/24/2018
PDUFA Goal Date	8/24/2019
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	Complete Response will be issued

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 (b) (4) %), 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. (b) (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 reference listed product on the applicant's 356h Form is AltaFluor Benox NDA 208582. NDA 208582 was also a 505b)(2) application which relied on the same published literature to establish safety and efficay.

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 6.1 Study endpoints
		□	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 6/11/2109:

The product, as historically marketed by the applicant, was labeled as Fluorescein Sodium 0.25% and Benoxinate Hydrochloride 0.4% Ophthalmic Solution and contains (b) (4) (b) (4) (b) (4) in order to (b) (4) 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]	(b) (4) %[2]	Active Ingredient	USP
benoxinate hydrochloride[1]	0.4%[3]	Active Ingredient	USP
Chlorobutanol	(b) (4)	(b) (4) Preservative	NF
Boric Acid		(b) (4)	NF
Povidone			USP
Hydrochloric Acid	As needed	pH Adjustment	NF
Water for injection (WFI)	(b) (4)	(b) (4)	USP
(b) (4)			
NF= National Formulary USP=United States Pharmacopeia Q.S.=Quantity Sufficient			

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

(b) (4) 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 (b) (4) cap.

Primary Container Closure System

Components		Description	DMF Number
Bottle	Size	6 cc	(b) (4)
	Description	Amber Glass Vial	
	(b) (4)		
	Colorant	N/A	
	Cross-Reference to Drawing	6 cc Bottle Drawing	
Closure	Size	20mm	
	Description	Polypropylene, Black Cap (b) (4)	
	Manufacturer	(b) (4)	
	(b) (4)		
	Cap Colorant		
	(b) (4)		
	(b) (4)		
	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: (b) (4)	NMT (b) (4)%
		Specified Unidentified Impurity (b) (4)	NMT (b) (4)%
		Specified Unidentified Impurity	NMT (b) (4)%
		Any Other Unspecified Impurity	NMT (b) (4)%
Total Impurities	23-T301	Release NMT (b) (4)%	Stability NMT (b) (4)%
Assay: Chlorobutanol[1]	23-T302	(b) (4)% 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 ± (b) (4).

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

Facilities Inspections

The Overall Recommendation for Facilities for NDA 211039 is Not Approvable.
Fluorescein Sodium (b) (4)% and Benoxinate Hydrochloride 0.4% Ophthalmic Solution is a sterile aqueous ophthalmic solution. There are (b) (4) (b) (4)

The facilities related to the Benoxinate Hydrochloride DS manufacturing and testing are acceptable based on the satisfactory compliance history and review of manufacturing capabilities. A PAI inspection was conducted for the Fluorescein Sodium DS manufacturer, (b) (4). The facility was found to be out of compliance because no corrective actions had been put in place to solve a previously noted (b) (4) issue. A withhold is recommended for this application.

A PAI inspection was conducted for the DP manufacturer, ALLIANCE MEDICAL (b) (4) (b) (4) Thus, a post-approval inspection will be recommended for the DP manufacturer.

The facility related to the DP testing, BAUSCH & LOMB, INC., FEI # 1317628, is acceptable based on the firm's compliance history and risk assessment. However, based on the recommendation from the inspector who conducted the PAI inspection for the DP manufacturer for this application, a PAI will be recommended after the CR letter is sent out to the sponsor due to the unsatisfactory compliance status of the Fluorescein Sodium DS manufacturer (b) (4).

Satisfactory resolution of the GMP deficiencies is required before this application may be approved.

Summary of 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	It is also the DP manufacturer. See below for the recommendation.
			High risk	***Not acceptable, based on PAI inspection conducted.***
			High risk	Acceptable, based on profile
			High risk	Acceptable, based on profile

Product Quality Recommendations and Conclusion on Approvability

Satisfactory information and responses have been submitted to support drug substance, drug product, and biopharmaceutics aspects.

The drug substance Fluorescein Sodium facility (b) (4) was recommended for a follow-up PAI inspection due to (b) (4) issue. The requested PAI inspection was conducted on (b) (4) and was classified as OAI. All the other facilities are acceptable based on the profile. Therefore, the overall recommendation of "withhold" was entered for the NDA into Panorama by OPF on 6/5/2019.

Additionally, two deficiencies from the manufacturing process are identified. Quality microbiology reviewer Dr. Valerie Huse has identified several outstanding deficiencies related to sterility of (b) (4) sterile dropper. These additional items are not approvability issues.

NDA 211039 is recommended for Complete Response from Product Quality perspective.

See Section 15 of this review for the full list of Recommended Comments to the Applicant.

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) 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 the studies in Table 9.1 which follows. 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%).

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 draft labeling on 12/14/2018.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

The Office of Prescription Drug Promotion (OPDP) completed a formal review of the package insert and labeling on 7/9/2019.

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. Labeling

Attached at the end of this review is revised labeling which is considered acceptable.

14. Postmarketing Recommendations

There are no postmarket risk evaluations or mitigation strategies recommended except the usual post-marketing collection and reporting of adverse experiences associated with the use of the drug product.

15. Recommended Comments to the Applicant

The following comments will be conveyed to the applicant in the Complete Response regulatory action letter:

FACILITIES INSPECTION
During a recent inspection of (b) (4) manufacturing facility for this NDA, 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

ADDITIONAL COMMENTS
We have the following comments/recommendations that are not approvability issues:

Manufacturing Process:

(1) We acknowledge your responses dated June 4, 2019. However, you did not provide the data requested for the two process deficiencies sent on May 22, 2019. We remind you that process validation is to confirm the process design and demonstrate that the commercial manufacturing process performs as expected (Guidance for Industry Process Validation: General Principles and Practices (2011)), (b) (4) (b) (4). Please provide data to resolve the two process deficiencies sent on May 22, 2019.

a) Please provide the compatibility data of the bulk solution with the (b) (4) to demonstrate that there are no significant changes in the physicochemical properties (b) (4) of the drug

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

b) Please provide the study report to establish the control strategy for (b) (4) (b) (4)

(2) The information request responses received by the Agency on 24 May 2019, stated that the (b) (4) (b) (4)

File (DMF) that includes the location in the DMF where the relevant information can be found.

(3) The Agency acknowledges the validation information and data provided for (b) (4) (b) (4)

(4) Please explain if the dropper (b) (4) (b) (4)

(b) (4)

(5) Please identify if the dropper assembly (b) (4)

(b) (4)

a) Description of the (b) (4)

(b) (4)

(b) (4)

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
07/18/2019 10:32:20 AM

WILEY A CHAMBERS
07/18/2019 12:50:24 PM

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	211039
Priority or Standard	S
Submit Date(s)	September 24, 2018
Received Date(s)	September 24, 2018
PDUFA Goal Date	July 24, 2019
Reviewer Name(s)	Lucious Lim, M.D., M.P.H.
Review Completion Date	June 14, 2019
Name	fluorescein sodium and benoxinate hydrochloride 0.3%/0.4% ophthalmic solution
Therapeutic Class	Disclosing agent and anesthetic combination
Applicant	Bausch Health Ireland Limited
Formulation(s)	Topical ophthalmic solution
Dosing Regimen	Instill 1 to 2 drops in eye prior to ophthalmic procedure
Indication(s)	For ophthalmic procedures requiring a disclosing agent in combination with a topical anesthetic
Intended Population(s)	Adult and pediatric patients

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 211039 is recommended for approval with the revised labeling identified in this review. The literature studies contained in this submission support the use of fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% for use in ophthalmic procedures requiring a disclosing agent in combination with a topical anesthetic. This is a 505(b)(2) application.

1.2 Risk Benefit Assessment

Benefit-Risk Integrated Assessment

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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no postmarket risk evaluations or mitigation strategies recommended except the usual post-marketing collection and reporting of adverse experiences associated with the use of the drug product.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no postmarket requirements or commitments recommended for this product.

1.5 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		[e.g., Sec 6.1 Study endpoints]
		□	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		[e.g., Sec 2.1 Analysis of Condition]
	□	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	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2 Introduction and Regulatory Background

2.1 Product Information

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. Fluorescein sodium as a single ingredient product has a long history of use as an unapproved product.

There is a United States Pharmacopeia (USP) monograph for Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution. Fluorescein sodium is a dye and is currently used extensively as a diagnostic tool. The purpose of the anesthetic in this combination product is to permit contact with the ocular surface and to reduce discomfort from the ophthalmic procedure. Fluorescein Sodium has been widely used for the examination of corneal epithelial integrity since 1882. Fluorescein sodium is currently used extensively as a diagnostic tool.

Fluorescein is also marketed as an injectable to be administered intravenously (IV). The IV form of fluorescein includes 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.

2.2 Tables of Currently Available Treatments for Proposed Indication

There is one approved product, Altafluor (fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.25%/0.4%), indicated for ophthalmic procedures requiring a disclosing agent in combination with an anesthetic agent. Altaflour was approved in December, 2016.

Following is a list of the fluorescein sodium and benoxinate hydrochloride (0.3%/0.4%) ophthalmic solution combination products that are currently marketed without approved new drug applications. Products such as these have been available since the mid-1960s.

- Fluress (Akorn)
- EyeFlur (Eye Supply)
- Flurox (Ocusoft)
- Fluoron (Eye Care & Cure)
- FluorBenox (Wilson)
- Fluorescein Sodium and Benoxinate Hydrochloride Solution (Altaire, Bausch & Lomb, Rosestone, Hub)

2.3 Availability of Proposed Active Ingredient in the United States

Fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% has been commercially available since at least the mid-1960s for use as a disclosing agent and topical anesthetic for ophthalmologic procedures.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no specific safety concerns that have arisen.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A pre-NDA meeting was held with the Agency for this product in August 2016.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of adequate quality and integrity to allow for a substantive review of the product.

3.2 Compliance with Good Clinical Practices

No 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%.

3.3 Financial Disclosures

No covered clinical studies are included in this application and, therefore, no financial certification or financial disclosure, as outlined in 21 CFR 54.4, was provided by the applicant. See Section 9.3.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The drug product that is the subject of this NDA is the same drug product and formulation as that previously marketed by Bausch & Lomb since 1994 as a USP compendial, unapproved drug product. The formulation was developed in 1993 as a copy of Fluress® Ophthalmic Solution, which was commercially available at the time and an unapproved drug product. The drug product is a sterile, preserved (chlorobutanol (b) (4)%), ophthalmic solution presented in a 6 cc amber glass bottle with a 20mm polypropylene black cap with a (b) (4)

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

Component	Formulation Quantity	Function	Quality Standard
Fluorescein Sodium[1]	(b) (4)	Active Ingredient	USP
benoxinate hydrochloride[1]	0.4%[3]	Active Ingredient	USP
Chlorobutanol	(b) (4)	Antimicrobial Preservative	NF
Boric Acid		(b) (4)	NF
Povidone			USP
Hydrochloric Acid	(b) (4)	pH Adjustment	NF
Water for injection (WFI)	(b) (4)	(b) (4)	USP
(b) (4)			

NF= National Formulary USP=United States Pharmacopeia Q.S.=Quantity Sufficient

4.2 Clinical Microbiology

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

4.3 Preclinical Pharmacology/Toxicology

No new nonclinical testing was conducted with fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% to support the submitted application. The Applicant is relying on the Agency's previous assessment of the safety of fluorescein sodium from the approved NDAs that contain this active pharmaceutical ingredient (Ak-Fluor 10% and 25% [NDA 022186] and Fluorescite [NDA 021980]) and submitted a summary of published literature for fluorescein sodium and benoxinate. Only limited information on the pharmacology and pharmacokinetics of the compound is in the summary provided by the Applicant.

4.4 Clinical Pharmacology

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

4.4.1 Mechanism of Action

Fluorescein sodium is a diagnostic dye which has been widely used to examine corneal integrity since 1882. Fluorescein sodium is a water soluble hydroxyxanthene dye with fluorescent properties. The drug response to electromagnetic radiation or light between the wavelengths of 465-490 nm is to emit a yellowish-green light at wavelengths of 520 – 530 nm.

Benoxinate hydrochloride is a topical anesthetic which binds to sodium channels and reversibly stabilizes the neuronal membrane which decreases its permeability to sodium ions. Depolarization of the neuronal membrane is inhibited, thereby blocking the initiation and conduction of nerve impulses.

4.4.2 Pharmacodynamics

Pharmacodynamic studies have not been conducted for this product by the applicant.

4.4.3 Pharmacokinetics

Pharmacokinetics studies have not been conducted for the product by the applicant.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5.1-1 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.

Reference	Subject Objective	Study Design Study Setting	No. of Patients/ Patient Demographics	Fluorescein and Benoxinate Ophthalmic Solution Information Manufacturer	Comments/ Findings
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.
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	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.

Reference	Subject Objective	Study Design Study Setting	No. of Patients/ Patient Demographics	Fluorescein and Benoxinate Ophthalmic Solution Information Manufacturer	Comments/ Findings
		Tanta University, Tanta, Egypt			

(b) (4)

Table 5.1-2 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 Pacific University College of Optometry, Forest Grove, OR Feb. 1979 – April 1979	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; Rose Bengal Manufacturer not specified	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
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	N= 72 GAT with Fluress N=33 pts presenting to the Pediatric Ophth. And Strabismus service	Fluress (fluorescein sodium and benoxinate HCl, USP) 0.3%/0.4% Akorn, Inc.[a]	None

		New England Eye Center, Tufts Univ. School of Medicine, Boston, MA Nov. 1995 and July 1996	Mean age: 14.5 Range (0-50 yrs) Adult/Ped: 4/29 Age 0-10 yrs: 7 Age 11-20 yrs: 12		
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)

Table 5.1-3 Supportive Clinical Safety and Efficacy Studies from Submitted Published Literature

Reference	**Subject Objective**	**Study Design Study Setting**	**No. of Patients/ Patient Demographics**	**Fluorescein and Benoxinate Ophthalmic Solution Information Manufacturer**	**Comments/ Findings**
Appelbaum et al. 1983	Assess adverse events associated with ophthalmic diagnostic drugs in clinical setting	Cross-sectional study N=12493 patients (eyes NR), including n=5153 patients who received Fluress (fluorescein-benoxinate solution) Southern CA College of Optometry, Fullerton, CA Oct 1981 – March 1982	N= 12493 M/F: 7350/ 5143 Age: NR [d] 698 pts rec'd Fluress age 0-20 yrs, (98 patients age 0-10 yrs)	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%; Hydroxyamphetamine 1.0% Manufacturer not specified [a]	Fluress applications recorded: 5153 total Age 0-10: 98 Age 11-20: 600 Age 21-30: 1148 Age 31-40: 717 Age 41-50: 890 Age 51-60: 804 Age >60: 896
Qureshi et al. 1996	Assess seasonal variation of IOP in healthy Chinese subjects	Prospective cohort study Shanghai Medical University, China	N= 103 (206 eyes) Healthy subjects underwent bimonthly assessments of IOP during a 14-	Fluress (fluorescein 0.3%- benoxinate 0.4%); Manufacturer not	Safety and tolerability not reported.

			month period 103 males Mean age: 26.3 Range: 21-30 yrs	specified [a]	
Yeung et al. 2000	Assess tolerability and corneal epithelial cell desquamation after GAT using fluoracaine or fluorox	Cross-sectional study Optometric Center of LA, Southern CA Colelge of Optometry Fullerton, CA	N= 30 healthy subjects (60 eyes) M/F: 12/18 Age: Healthy mean 27 y (range 18-42 yrs)	Fluorox (0.3% fluorescein- 0.4% benoxinate) Fluorocaine (0.3% fluorescein- 0.5% proparacaine) Altaire Pharmaceuticals	None.
Korn et al. 2005	Management of patient with a corneal perforation from the bite of a boa constrictor	Case report Shiley Eye Center, University of CA at San Diego San Diego, CA	N= 1 patient 30 yo male	Benoxinate 0.4%-fluorescein 0.3% ophthalmic solution Manufacturer not specified	Safety and tolerability not reported.
Liu et al. 2005	Assess whether abnormal tear film dynamics contribute to floppy eyelid syndrome (FES)	Cross-sectional study Bascom Palmer Eye Inst., Univ. of Miami, School of Medicine Miami, FL	N= 16 pts (32 eyes) with FES	Fluress (fluorescein 0.3%- benoxinate 0.4%); Akorn, Inc. [a]	Safety and tolerability not reported.
Semes t. al, 2006	Assess relationship between race, iris color, CCT and IOP	Cross-sectional study Department of Optometry, University of Alabama, Birmingham, AL	N=66 M/F: 12/54 Age: 18-74	Fluress (fluorescein 0.3%- benoxinate 0.4%) Akorn Flurox (fluorescein 0.3%- benoxinate 0.4%) oCuSOFT	• No statistically significant difference in pachymetry measurements, CCT, or CCT adjusted IOP was observed between iris colors
Broman et al., 2007	Estimate relationships between ocular parameters and IOP	Prospective, non-randomized, unmasked Johns Hopkins School of Public Health, Baltimore, MD	N=171 (342 eyes) analyzed Age: 40-80 yrs	Fluress (fluorescein 0.3%- benoxinate 0.4%) Bausch & Lomb	• IOP measurements were lowest for Tono-Pen, highest for ORA[d] and GAT closest to mean IOP of the 3 instruments. • A 10µm increase in CCT[e] was associated with an increase of 0.79mmHg. • GAT was least affected by CCT
Erickson et al, 2010	Evaluation of ocular pulse amplitude and risk of glaucoma	Prospective, non-randomized, unmasked	N=110 (220eyes) Age: >18 yrs	Flurox (fluorescein 0.3%- benoxinate 0.4%)	• DCT[f] measurements were on average,

		Pacific University College of Optometry, Forest Grove, Oregon		oCuSOFT	0.9 mmHg lower than GAT in OD and 0.7 mmHg lower in OS. • Both methods correlated with CCT and neither were significantly influenced by corneal curvature or refractive error.
Realini et al. 2010	Assess repeatability of diurnal IOP patterns in healthy subjects	Prospective cohort study West Virginia University Eye Inst. Morgantown, WV	N= 40 healthy adults (80 eyes)	Fluress (fluorescein 0.3%- benoxinate 0.4%); Akorn, Inc. [a]	Safety and tolerability not reported.
Pekmeczi et al. 2011	Assess whether order of measurement between OD and OS affects observed IOP	Randomized, unmasked Washington University St. Louis, Mo	N=105 (210 eyes had GAT IOP assessed repeatedly M/F: 41/64 Age: 39 yrs (mean) No pediatric pts.	Benoxinate 0.4%-fluorescein 0.3% ophthalmic solution Manufacturer not specified [d]	Safety and tolerability not reported.
Johannesson et. al., 2014	Assess effects of topical anesthetics and repeated tonometry on IOP	Prospective, consecutive series, unmasked Umea University, Umea, Sweden	N=6 (12 eyes)	Fluress (fluorescein 0.3%- benoxinate 0.4%) Abigo, Askim, Sweden	Significant reduction in IOP with both benoxinate and tetracaine but significantly greater reduction with benoxinate
Dosunmu et al. 2014a	Effect of repeated measurements of IOP with GAT and Tono-Pen in normal/ adolescent children	Prospective, non-randomized, unmasked Duke University Eye Center Durham, NC	N=10 (20 eyes) M/F: 6/4 Age: 6-10 yrs	fluorescein sodium 0.3% and benoxinate HCl 0.4% Manufacturer not specified	Neither sequential Icare measurements prior to topical anesthetic produced a statistically or clinically significant change in measured IOP by rebound tonometry. IOP values between Icare and GAT showed that mean IOP values with GAT were lower

(b) (4)

Table 5.1-4 Key Literature References Supporting Fluorescein Sodium Concentration

Reference	Study Objective	Study Description	Study Drug Dose	Study Findings
Moses, R.A. 1960	Evaluate the optimum concentration and pH of fluorescein solutions in applanation tonometry.	Fluorescein solutions of various concentrations were prepared and used to perform applanation tonometry on a Lucite ball (diameter 25 mm) held by a clamp to the headrest of the Haag-Streit slit lamp microscope. The tonometer prism was held against the ball with a force of 1 gm. A drop of fluorescein solution was placed between the ball and prism. The resulting pattern was viewed through the slit lamp to calculate the applanated area and mires. The error in IOP caused by the different applanated areas by the different solutions was calculated.	Various concentrations of fluorescein were prepared by diluting stock 2.0% fluorescein with • Normal saline (NS), • Equal parts NS and 0.2% Novesine [a], • Novesine • Equal parts NS and 0.5% Ophthaine [b], • 0.5% Ophthaine and • Seven parts phosphate buffer (ph 7) and Ophthaine	• Goldmann applanation tonometry (GAT) measurements were most accurate with fluorescein solution concentrations of 0.5% to 0.125% regardless of the diluent used. • GAT with an insufficient concentration of fluorescein in the tear fluid will underestimate IOP. • Topical anesthetic solutions tested quench much of the fluorescence of fluorescein.
Grant, W.M. 1963	To determine the optimum concentration of fluorescein to be used in Goldmann applanation tonometry	Sodium fluorescein solutions of 0.125, 0.3, 0.5 and 2.0 percent were instilled after one drop of proparacaine in a series of 200 patients to determine which concentration provided the best tonometer-cornea interface and patient experience.	Sodium fluorescein solutions of 0.125, 0.3, 0.5 and 2.0 percent prepared by Barnes-Hind Laboratories, Sunnyvale, CA	The 0.3% sodium fluorescein gave the best results. The 0.125% and 0.5% solutions were usable but produced less distinct mires. interference with visualization in gonioscopy was present with the 0.5% and 2.0%. Discoloration of the lid margins was unacceptable with the 2.0% > 0.5% solutions.
Fenton, P.J. 1965	To determine the best anesthetic to mix with fluorescein solution and the best concentration of each	Mixtures of 0.125% fluorescein and multiple anesthetics (lignocaine HCl, cocaine, amethocaine, butacaine proparacaine and Novesine (benoxinate) 0.4%) were prepared in neutral glass bottles. The solutions were observed at 25C for 1 hour. Those with minimal precipitates were then observed at 4C, 25C and 37C for 24 hours and 1 week.	0.125% sodium fluorescein multiple anesthetics	The recommended mixture was 0.3% Novesine (benoxinate) and 0.125% fluorescein because of good, quick anesthetic action, adequate fluorescent mires, no vasodilator/vasoconstrictor activity, no effect of pupil, low corneal/conjunctival toxicity and no precipitate formation.

Reference	Study Objective	Study Description	Study Drug Dose	Study Findings
Lux et al. 2003	Comparative bioavailability of 3 drops of fluorescein eye drops with a single dose of lyophilizate	In randomized, open-label study 22 healthy volunteers applied single lysophilisate to one eye and 3 drops fluorescein to fellow eye. The fluorescein dose of lyophilizate was 204 mg corresponding to 3 drops of 40 ml fluorescein SE Thilo 0.17% (Alcon). Fluorophotometry was performed before and +15, 30, 45, 60, 120, 180, 240, 300, 360, 420 minutes after application. Fluorescein concentrations of corneal stroma and mid-anterior chamber were analysed.	Fluorescein supplied by Alcon, Germany	Cornea and anterior chamber mean values were significantly higher ($p<0.18$) in the lyophilizate group up to 7 hrs after application with the exception of the 45-minute time point. Mean fluorescein bioavailability was up 11 times higher in the cornea and up 70 8.7 times higher in the anterior chamber compared with the eye drops.

a Novesine was a benoxinate HCl ophthalmic solution, 0.4% manufactured by Wander [Germany]
b Ophthaine was a 0.5% proparacaine ophthalmic solution manufactured by Squibb

Reviewer's Comment: *Sodium fluorescein has been tested and utilized as a disclosing agent for Goldmann applanation tonometry at concentrations ranging from 0% to 2.0%. The 0.125% concentration has produced satisfactory results. The literature describes that the best results were achieved with the 0.3% fluorescein sodium ophthalmic solution.*

Table 5.1-5 Key Literature References Supporting Benoxinate Hydrochloride Concentration

Reference	Study Objective	Study Description	Study Drug Dose	Study Findings
Schlegel H.E. and Swan, K.C. 1954	Evaluation of improved methods and agents for inducing anesthesia local to the eye and its adnexa for clinical (office) use.	Report of a series of nonclinical and clinical investigations of benoxinate performed by multiple researchers – including the Univ. or Oregon Medical School. At the Univ. of Oregon Medical School 1000 patients in the eye clinic were administered 0.1% to 0.5% benoxinate.	Benoxinate 0.1%, 0.2%, 0.4% and 0.5%	• A single instillation of 0.1% permitted tonometry within 60-90 seconds. Duration of anesthesia, 10-15 min. • A single instillation of 0.2% induced more consistent anesthesia but required multiple instillations for minor surgery i.e., suture removal, removal of embedded corneal foreign body. • 0.4% benoxinate deemed most suitable for routine office use – produced adequate anesthesia for office use and isotonic so produced very little irritation. • 1 ml instilled in the lacrimal sac produced excellent anesthesia for probing and irrigation. • 0.5% benoxinate solution was well tolerated and induced conjunctival and corneal anesthesia lasting 20-30 min • 0.4% benoxinate solns not easily contaminated with bacteria, even when left open for 1 week.
Emmerich, et al. 1955	To evaluate experimentally the clinical utility of dorsacaine (benoxinate HCl 0.4%)	Subjective reactions to 0.2% and 0.4% benoxinate were evaluated in 408 unselected patients from the glaucoma and emergency services at NYEEI.	Benoxinate 0.2% and 0.4%	• Irritation directly proportional to amount of the anesthetic and concentration instilled. • Confirmation that 0.4 % benoxinate was effective for tonometry, CLs fitting, probing and irrigation of lacrimal sac, removal of corneal FBs, gonioscopy, excision of chalazia, and suture removal.

Reference	Study Objective	Study Description	Study Drug Dose	Study Findings
Polse et al. 1978	To describe the dose response effects of corneal anesthetics	The changes in corneal sensitivity for 3 concentrations each of proparacaine and of benoxinate were determined by monitoring changes in corneal sensitivity psychophysically, using a modified Cochet-Bonnet esthesiometer. Doses required to produce sufficient anesthesia for GAT were also determined. (N=7)	Benoxinate 0.1%, 0.2% and 0.4% (only the amount of active ingredient was changed to achieve the required concentration)	• Threshold sensitivity 75 mg/mm^2 before GAT could be performed. • Tonometry can be performed with as little as 1 drop of 0.1% benoxinate. • 0.2% benoxinate provides sufficient GAT threshold anesthesia for long enough (2-4 min) to be clinically useful. • Duration of action of 0.4% benoxinate is ≥ 45 min compared with approx. 33 min for 0.2% benoxinate. Thus, 0.4% benoxinate is appropriate for longer more involved procedures (i.e., gonioscopy, FB removal).

Reviewer's Comment: *Benoxinate hydrochloride has been tested as a topical ophthalmic anesthetic for Goldmann applanation tonometry and general office use for ophthalmology at concentrations ranging from 0.1% to 0.5%. The 0.4% concentration produced the best results for Goldmann applanation tonometry and other ophthalmic office procedures (i.e., gonioscopy, foreign body removal).*

5.2 Review Strategy

This is a 505(b)(2) application primarily based on literature reports provided by a literature review conducted by the applicant.

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 0.3%/0.4% in providing adequate visualization and topical anesthesia in pediatric patients form the primary basis of support for efficacy in the pediatric population.

Twelve additional clinical studies from the published literature were submitted and provide supportive safety and efficacy information for fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% for applanation tonometry and other procedures.

6 Efficacy Summary

There is adequate support from the literature to support the use of this product for ophthalmic procedures requiring a disclosing agent in combination with an anesthetic agent. The support for efficacy is provided in the following references: Hales 1967, Quickert 1967, Katz 1976, Bright 1981, Jose 1983 and Ng 2006.

The adequacy of fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% was assessed during the ophthalmic examination within minutes after drop instillation in that Goldmann applanation tonometry was able to be performed.

The overall age range of patients from the key efficacy studies (Tables 5.1-1 and 5.1-2) 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.

Two references (Moses 1960 and Fenton 1965) tested a range of concentrations of fluorescein sodium and benoxinate hydrochloride ophthalmic solutions. Concentrations as low as 0.125% fluorescein sodium and 0.1% benoxinate hydrochloride were effective at providing adequate fluorescence/visualization and anesthesia.

The effect of the fluorescein sodium as a disclosing agent occurs immediately upon instillation and lasts for 10 to 15 minutes.

The anesthetic effect of the benoxinate hydrochloride occurs within 60 – 90 seconds and lasts up to 45 minutes.

7 Review of Safety

Safety Summary
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.

7.1 Methods

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.

Studies/Clinical Trials Used to Evaluate Safety

A review of the submitted literature reveals that fluorescein sodium and benoxinate hydrochloride ophthalmic solution 0.3%/0.4% is safe for the proposed indication in adult and pediatric patients.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure and Demographics of Target Populations

Fluorescein and Benoxinate Ophthalmic Solution (0.3%/0.4%) has been commercially available since the late 1960s and widely used in routine eye examinations and ophthalmic procedures which required a disclosing agent and topical anesthetic. Due to the long history and frequent use of fluorescein and benoxinate ophthalmic solution (0.3%/0.4%), there has been adequate exposure for safety evaluation.

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 the studies in Table 7.2.1-1. 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.

The studies which did report of the safety and/or tolerability included six single-dose studies and a multiple dose study in which patients received six does per eye per day on Days 1, 8, and 15 for a total of 18 doses per eye during the 15 day study.

Table 7.2.1-1 Key Studies which Reported on the Safety and/or Tolerability of Fluorescein and Benoxinate Ophthalmic Solution 0.3%/0.4% [a]

Reference	Treatment Arm	No. of Patients Enrolled/ Completed	Fluorescein sodium and benoxinate HCl ophthalmic solution 0.3%/ 0.4%		Comparator	
			Adverse Events	Tolerability	Adverse Events	Tolerability
Hales 1967	GAT with fluorescein 0.3% - benoxinate 0.4% ophthalmic solution	1381 / 1381	No allergic rxns No toxic rxns No infections	Some patients (n=NR) experienced a burning sensation in eye after instillation. Discomfort was described as similar to that seen with proparacaine HCl and less than that seen with tetracaine HCl	N/A	N/A
Quickert 1967	GAT with fluorescein 0.3%-benoxinate 0.4% ophthalmic solution Comparator: proparacaine 0.5% and fluorescein 0.3% ophthalmic solution	50 /50 50 / 50	NR	Some patients reported mild to moderate stinging (n=17; 34.0%) or marked stinging (n=3; 6.0%) after instillation	NR	Some patients reported mild to moderate stinging (n=13; 26.0%) or marked stinging (n=2; 4.0%) after instillation.
Katz et al. 1976	GAT with fluorescein 0.3%-benoxinate 0.4% ophthalmic solution	30 / 30	Some (n=NR) patients experienced bulbar conjunctiva erythema and/or punctate keratitis	NR	N/A	N/A
Yolton et al. 1980	Benoxinate 0.4% and 0.3% fluorescein ophthalmic solution	2323 applications (patient number NR)	Benoxinate 0.4% and 0.3% fluorescein ophthalmic solution had a side effect rate of 1.7 per 1000 applications. AEs: 2 cases of mild conjunctival infxn (self-limited) In 236 applications of benoxinate 0.4% and 0.3% fluorescein ophthalmic soln. in pts age 0-20, there were 2 cases of mild conjunctival infxn (self-limited)	NR	NR	NR
Appelbaum et al. 1983	Benoxinate 0.4% and 0.3% fluorescein ophthalmic	5153 / 5153	Patients receiving benoxinate 0.4% and 0.3% fluorescein ophthalmic solution experienced 5 AEs:	NR	NR	NR

Reference	Treatment Arm	No. of Patients Enrolled/ Completed	Fluorescein sodium and benoxinate HCl ophthalmic solution 0.3%/ 0.4%		Comparator	
			Adverse Events	Tolerability	Adverse Events	Tolerability
	solution		IOP elevation that resolved in 30 min, Stinging that resolved quickly, Coldness/dizziness/fainting that resolved in 10 min. Burning/itching morning after tx resolved in 48 h. Dull ache, resolved in 24 h. Of the 698 pts age 0-20 who rec'd benoxinate 0.4% and fluorescein 0/25% only 1 experienced an AE.			
Yeung et al. 2000	Fluorescein 0.3% - benoxinate 0.4% ophthalmic solution Comparator: Proparacaine 0.5% and fluorescein 0.3% ophthalmic solution	30 / 30 30/30	Compared to eyes that rec'd benoxinate 0.4% and 0.3% fluorescein ophthalmic solution, those that received proparacaine 0.5% and 0.3% fluorescein ophthalmic solution had clinically and statistically more severe types of corneal desquamation (p=0.04 at 3 min, p<0.001 at 5, 7, 10, 15, and 20 min).	47% of pts reported more stinging in the eye that rec'd benoxinate 0.4% and 0.3% fluorescein ophthalmic soln, and 30% reported no difference	Caused superficial micropunctate keratitis in 16%-30% of cornea	23% reported more stinging in the eye that rec'd proparacaine 0.5% and 0.3% fluorescein ophthalmic soln.
Ng et al. 2006	Benoxinate 0.4% and 0.3% fluorescein ophthalmic soln. Comparator: Benoxinate 0.4% and 0.35% fluorexon disodium	67 / 67	Corneal staining was present in some (n=11; 16.4%) patients following GAT according to physician survey	Some pts reported discomfort (n=20; 29.9%), soreness or irritation (n=10; 14.9%), and burning or stinging (n=17; 25.4%) after instillation	Corneal staining was present in some (n=4; 6.0%) patients following GAT according to physician survey	Some patients reported discomfort (n=13; 19.4%), soreness or irritation (n=8; 11.9%), and burning or stinging (n=11; 16.4%) after instillation.

GAT = Goldmann applanation tonometry; NR = Not reported
[a] Taken from the studies listed in Section 5.1.

7.2.3 Special Animal and/or In Vitro Testing

Special animal /*in vitro* testing has not been conducted for this product.

7.2.4 Routine Clinical Testing

Routine clinical testing has not been conducted for this product.

7.2.5 Metabolic, Clearance, and Interaction Workup

Metabolic, clearance, and interaction workups were not conducted for this product.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths attributable to fluorescein sodium and benoxinate hydrochloride ophthalmic solution (0.3%/0.4%) reported in the published literature reports.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events attributable to fluorescein sodium and benoxinate hydrochloride ophthalmic solution (0.3%/0.4%) reported in the published literature.

7.3.3 Dropouts and/or Discontinuations

The effect of fluorescein sodium and benoxinate hydrochloride ophthalmic solution (0.3%/0.4%) was seen within seconds of instillation and coincident with the performance of ophthalmic procedures. Therefore, all subjects in the studies were available for evaluation.

7.3.4 Significant Adverse Events

There were no severe or significant adverse events reported in the published literature.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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 literature reports of the clinical studies which did report on these adverse reactions were described in Table 7.2.1-1 and were reviewed in depth.

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.

7.4.2 Laboratory Findings

There was no information on laboratory findings associated with the use of fluorescein sodium and benoxinate hydrochloride ophthalmic solution (0.3%/0.4%) available.

7.4.3 Vital Signs

There was no information on vital signs associated with the use of fluorescein sodium and benoxinate hydrochloride ophthalmic solution (0.3%/0.4%) available.

7.4.4 Electrocardiograms (ECGs)

There was no information on electrocardiograms associated with the use of fluorescein sodium and benoxinate hydrochloride ophthalmic solution (0.3%/0.4%) available.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies/ clinical trials were conducted by the Applicant.

7.4.6 Immunogenicity

Allergic reactions to topical fluorescein sodium and benoxinate hydrochloride ophthalmic solution (0.3%/0.4%) have not been specifically reported in the literature.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events- Not applicable.

7.5.2 Time Dependency for Adverse Events- Not applicable.

7.5.3 Drug-Demographic Interactions- Not applicable.

7.5.4 Drug-Disease Interactions- Not applicable.

7.5.5 Drug-Drug Interactions- Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity- Not applicable.

7.6.2 Human Reproduction and Pregnancy Data- Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth- Given the short term episodic use of the product, no long term studies of its effect on growth have been performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound- When topical anesthetics are used outside of this setting with repeated instillations, cases of corneal ulceration, thinning and perforation, some requiring full thickness corneal transplantation has occurred.

7.7 Safety Update

The 120 Day Safety Update report has been submitted. No new issues related to safety or efficacy were identified.

8 Postmarket Experience

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.
Valeant has provided a summary table providing distribution totals for the years 2009 to 2017, indicating both total number of units distributed annually:

Table 8-1 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**

Table 8-2
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**

Reviewer's Comment: *The most common 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%).*

Food and Drug Administration's Adverse Event Reporting System (FAERS) Summary

Bausch Health conducted a review of all adverse event (AE) reports using the product terms fluorescein and benoxinate, submitted to the Food and Drug Administration's Adverse Event Reporting System (FAERS) database. The review identified 76 reported cases of which 61 were reported as serious and 2 deaths.

The 2 deaths were associated with the use of fluorescein injection for angiography. Case ID 6211144: A 74-year-old male suffered anaphylactic shock, hypopnea, and loss of consciousness following a retinal angiogram. Case ID 7703198: A 63-year-old male experienced abnormal feelings and cardiac arrest following retinal angiography for diabetic retinopathy.

Reviewer's Comments: *The two deaths occurred following intravenous administration of fluorescein.*

Table 8-3 FAERS Report of Adverse Events Reported by ≥ 2 % for Fluorescein Sodium and Benoxinate Hydrochloride

AE Term	Number of Reports
OCULAR	
Vision blurred	4
Erythema	3
Burning Sensation	3
Visual acuity reduced	3
Eye pain	2
Vision impairment	2
Conjunctivitis	2
Contrast media reaction	2
Cataract	2
Blindness	2
Age related macular degeneration	2
Macular edema	2
NON-OCULAR	
Pruritus	9
Dyspnea	8
Drug hypersensitivity	8
Urticaria	7
Nausea	7
Hyperdrosis	7
Dizziness	7
Anaphylactic reaction	6
Rash	5
Loss of consciousness	5
Hypotension	4
Pain	4
Headache	4
Felling abnormal	4
Syncope	4
Anaphylactic shock	4
Cardio-respiratory arrest	4
Chest pain	3
Fatigue	3
Chest discomfort	3
Confusional state	3
Cough	3
Vomiting	3
Blood pressure decreased	3
Flushing	3
Throat irritation	3
Feeling hot	2
Angina pectoris	2
Swelling face	2
Blood pressure increased	2
Chills	2
Pallor	2
Bradycardia	2

AE Term	Number of Reports
Malaise	2
Anxiety	2
Diarrhea	2
Dry mouth	2
Drug interaction	2
Pharyngeal edema	2
Rash erythematous	2
Cardiac disorder	2
Therapy non-responder	2
Cold sweat	2
Documented hypersensitivity to administered product	2
Bronchospasm	2
Contrast media allergy	2
TOTAL	**76**

Reviewer's Comment: *The most common ocular adverse events are blurred vision (5%), erythema (4%), burning sensation (4%), and reduced visual acuity (4%). The most common non-ocular adverse events are pruritus (12%), dyspnea (11%), and dry hypersensitivity (11%).*

9 Appendices

9.1 Literature Review References

A literature review did not identify additional relevant materials for this application.

9.2 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.

9.3 Labeling Recommendations

Following is the applicant's draft labeling with recommended Agency revisions.

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

Container Label

1. The name of the product should be revised to be consistent with the prescribing information (PI): Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution, USP 0.3%/0.4%.

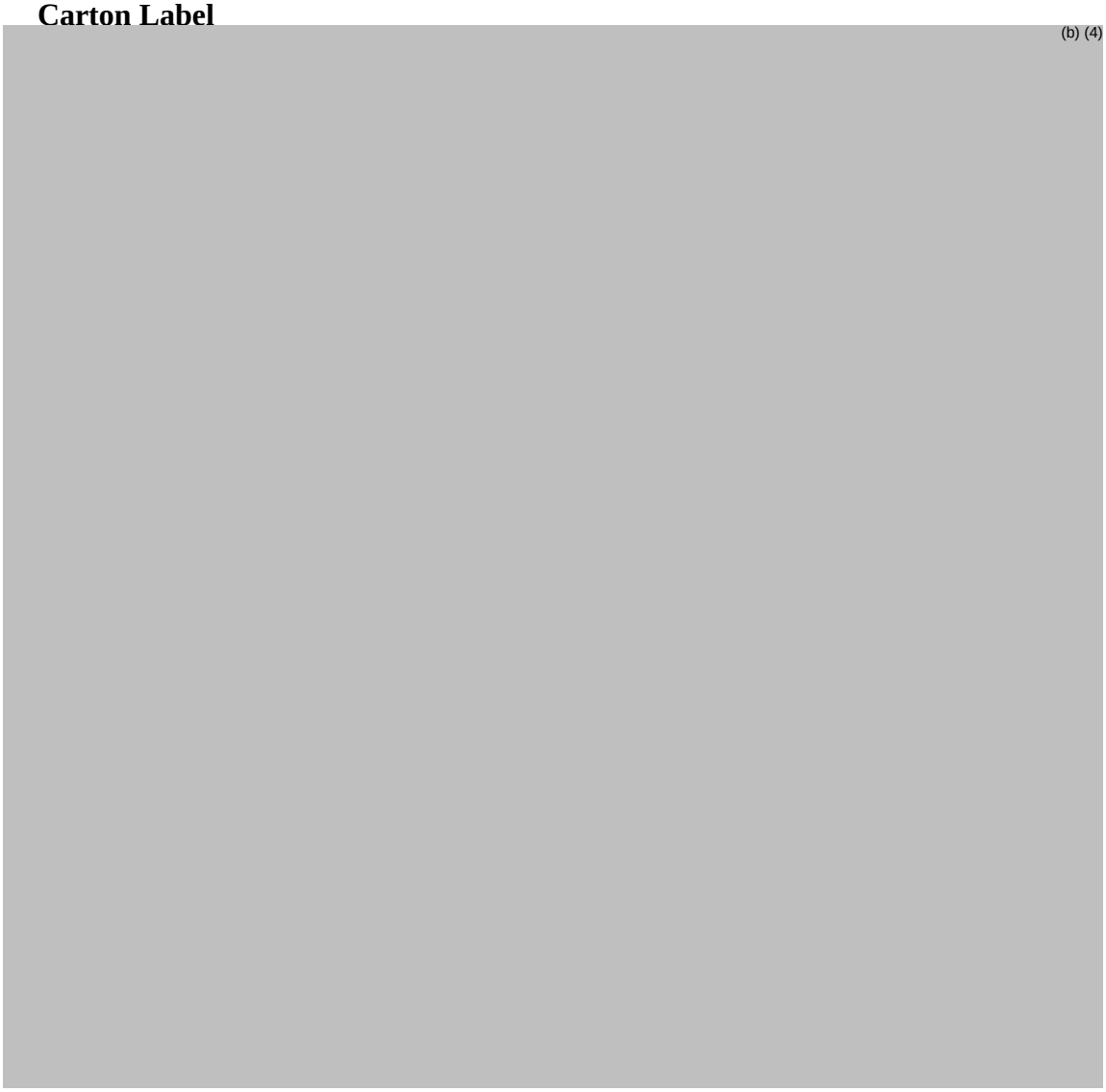
2 (b) (4) should be revised to read, "FOR TOPICAL OPHTHALMIC USE."

3. The NDC listed here is not consistent with NDC in the prescribing information (PI). Applicant should clarify which NDC they intend to include and ensure the NDC is consistent throughout all labeling (i.e., prescribing information, container label, and carton labeling).

4. Storage conditions should be revised to be consistent with the consistent with the prescribing information (PI).

5. "Each mL Contains…" should be revised consistent with the prescribing information (PI).

Carton Label



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4. Storage conditions should be revised to be consistent with the consistent with the prescribing information (PI).

5. "Each mL Contains…" should be revised consistent with the prescribing information (PI).

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/

LUCIOUS LIM
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