CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206911Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review for NDA 206911

Date	April 8, 2016
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	206911
Applicant	InSite Vision Incorporated
Date of Submission	June 10, 2015
PDUFA Goal Date	April 10, 2016
Type of Application	505(b)(2)
Name	BromSite (bromfenac ophthalmic solution) 0.075%
Dosage forms / Strength	Topical ophthalmic solution
Proposed Indication(s)	Treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery
Recommended:	Recommended for Approval

1. Introduction

BromSite is a topical ophthalmic solution of 0.075% bromfenac, a nonsteroidal anti-inflammatory drug (NSAID), formulated in DuraSite®, InSite Vision's drug delivery vehicle. It is a sterile preserved, multi-dose eye drop intended for the treatment of post-surgical inflammation and prevention of ocular pain in patients (b) (4) cataract (b) (4) surgery. BromSite is administered twice a day for 16 days (the day before surgery, the day of surgery, and 14 days after cataract surgery).

BromSite (bromfenac ophthalmic solution) 0.075% was called ISV-303 during its drug development.

This is a 505(b)(2) application. NDA 206911 (BromSite) relies on FDA's previous finding of safety for the listed drug Xibrom/Bromday (NDA 21664), specifically nonclinical information. The applicant conducted a nonclinical ocular toxicity study in rabbits to qualify impurities, and provide ocular toxicity bridging data. In this study, it was demonstrated that the plasma levels of bromfenac following topical ocular administration of BromSite were well below those used in non-clinical studies conducted to support the listed drug Xibrom. This supports reliance on the nonclinical data used to support approval of Xibrom to support the approval of BromSite.

2. Background

The primary support for efficacy and safety for BromSite (bromfenac ophthalmic solution) 0.075% were two Phase 3, randomized double-masked studies to compare the ocular safety, tolerability, and efficacy of ISV-303 (0.075% bromfenac in DuraSite) to DuraSite vehicle in cataract surgery subjects.

A Pre-IND (107723) meeting was held on 4/26/10; an End of Phase 2 (EOP2) meeting was held on 2/17/12; and two Pre-NDA meetings were held, one on 1/13/14, and one on 4/15/14.

Currently Available Treatments (Approved Drugs) for Proposed Indication

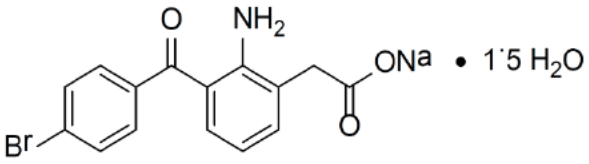
NDA	Drug	Indication
22-212	Difluprednate ophthalmic emulsion 0.05% (Durezol)	DUREZOL is a topical corticosteroid that is indicated for the treatment of inflammation and pain associated with ocular surgery. DUREZOL is also indicated for the treatment of endogenous anterior uveitis.
202-872	Loteprednol etabonate ophthalmic gel 0.5% (Lotemax)	LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.
20-474	Rimexolone ophthalmic suspension 1% (Vexol)	VEXOL 1% (rimexolone ophthalmic suspension) is indicated for the treatment of post-operative inflammation following ocular surgery and in the treatment of anterior uveitis.
203-168	Bromfenac ophthalmic solution 0.07% (Prolensa)	PROLENSA is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.
21-664*	Bromfenac sodium ophthalmic solution 0.09% (Xibrom)	XIBROM is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-664 201-211 202-030 203-395	Bromfenac sodium ophthalmic solution 0.09% (Bromday)	BROMDAY is a NSAID indicated for the treatment of post-operative inflammation and reduction of ocular pain in patients who have undergone cataract extraction.
21-862	Nepafenac ophthalmic suspension 0.1% (Nevanac)	NEVANAC ophthalmic suspension is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
203-491	Nepafenac ophthalmic suspension 0.3% (Ilevro)	ILEVRO (nepafenac ophthalmic suspension), 0.3% is a NSAID indicated for the treatment of pain and inflammation associated with cataract surgery.
19-700	Ketorolac tromethamine ophthalmic solution 0.5% (Acular)	ACULAR ophthalmic solution is a NSAID indicated for: • The treatment of inflammation following cataract surgery • The temporary relief of ocular itching due to seasonal allergic conjunctivitis
22-427	Ketorolac tromethamine ophthalmic solution 0.45% (Acuvail)	ACUVAIL ophthalmic solution is a NSAID indicated for the treatment of pain and inflammation following cataract surgery.
20-037	Diclofenac sodium ophthalmic solution 0.1% (Voltaren Ophthalmic)	VOLTAREN ophthalmic is indicated for the treatment of post-operative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.

*NDA 21-664 is the reference listed drug for this 505(b) (2) application.

3. CMC

DRUG SUBSTANCE:

The applicant cross-referenced the CMC information for bromfenac sodium drug substance to DMF [redacted] DMF [redacted] was reviewed and was found adequate to support NDA 206911.



Bromfenac sodium (sodium 2-amino-3-(4-bromobenzoyl)phenylacetate sesquihydrate) is a member of the phenylacetic acid class of non-steroidal anti-inflammatory drugs (NSAIDs) and has been used in other FDA approved ophthalmic solutions (Prolensa, Bromday, and Xibrom). This drug substance is a bright orange to yellow powder of a [redacted]. Bromfenac is adequately soluble (≥ 0.5% w/w) over the pH range of 7.2 to 10.2 to achieve the target drug product concentration of 0.075%. Stability data from the DMF holder support a retest period of [redacted] months for bromfenac sodium drug substance manufactured at [redacted]. and stored at [redacted]

Table 3.2.S.4.1-1: InSite Vision Raw Material Specification for Bromfenac Sodium Sesquihydrate Drug Substance Supplied by (b) (4)

Test	Test Method	Acceptance Criteria
Appearance	TM224	Bright orange to yellow powder
Identification by IR	USP <197K>	Pass
Indentification by HPLC retention	TM057	Pass
Identification sodium (flame)	USP <191>	Pass
pH	TM226	(b) (4)
Water	USP <921>	
Heavy Metals	USP <231> Method II	NMT (b) (4)
Assay ((b) (4)	TM057	(b) (4)
Related Substances	TM057	Impurity (b) (4) NMT (b) (4) Impurity (b) (4) NMT (b) (4) Single impurity NMT (b) (4) Total impurities NMT (b) (4)
Residual Solvents	Acceptance is based on manufacturer's Certificate of Analysis	(b) (4)
(b) (4)	Acceptance is based on manufacturer's Certificate of Analysis	NMT (b) (4)

NMT = Not more than (b) (4)

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Bromfenac ophthalmic solution, 0.075% drug product is a sterile, preserved, (b) (4) viscous, multidose eye drop in 7.5 mL white low density polyethylene (LDPE) bottles (5 mL fill) with clear LDPE dropper tips, gray high density polyethylene (HDPE) dropper caps and white LDPE tamper-evident ove (b) (4). Additionally, each bottle is enclosed in a (b) (4) sealed laminated (b) (4) foil pouch.

The active ingredient is bromfenac sodium (b) (4) Each mL of the drug product contains 0.76 mg of bromfenac as free acid, which is equivalent to 0.81 mg of bromfenac sodium. A list of all components of the bromfenac solution with their amounts, functions and reference to their quality standard is summarized in the table below. All the excipients are compendial. DuraSite, InSite Vision's drug delivery system, is composed of (b) (4) . DuraSite has been used in an approved drug product, AzaSite, NDA# 50810.

Ingredients	Concentration (%w/w)	Function
Bromfenac Sodium Sesquihydrate	0.075	API
Boric Acid, NF	(b) (4)	
Sodium Borate, NF		
Citric Acid Anhydrous, USP		
Sodium Citrate Dihydrate, USP		
Poloxamer 407, NF		
Benzalkonium Chloride, NF	0.005	(b) (4) preservative
Polycarbophil, USP	(b) (4)	
Sodium Chloride, USP		
Edetate Disodium Dihydrate, USP		
(b) (4) Sodium Hydroxide, NF	Adjust to pH 8.3	pH adjusting agent
Water For Injection, USP	(b) (4)	

CONTAINER CLOSURE SYSTEM:
The proposed drug product is packaged in a 7.5 mL white LDPE bottle with a clear LDPE dropper tip and a gray HDPE cap.

The components of the container/closure system used are summarized in the table below. The 7.5 mL bottle (b) (4) (b) (4) he dropper tip is made from clear LDPE (b) (4) The cap is a gray colored eyedropper cap made from HDPE using (b) (4) for HDPE (b) (4) are submitted. (b) (4)

Table 3.2.P.7-1: Container Closure System Components

Components Description	Material	Material Supplier	Component Manufacturer
White 7.5 mL bottle and tamper-evident over [redacted]	[redacted]	[redacted]	[redacted]
[redacted] clear dropper tip			
[redacted] gray HDPE cap			
Bottle Label			
Secondary Laminated Foil Pouch			
Tertiary Packaging			

The applicant carried out a dose reproducibility study on the 3 registration stability batches (00313B, 00131C and 00313D). The average and range of drop sizes measured were very similar from the studied 3 batches with 2 fill volumes (2.5 mL and 5 mL). The average drop size is [redacted] mg.

PROPOSED REGULATORY SPECIFICATIONS:

Table 3.2.P.5.1-1 Proposed Release Specifications for ISV-303 (0.075% Bromfenac)

Attribute	Method	Acceptance Criterion
Identification (Bromfenac) HPLC Retention Time	TM058	Pass
Identification (Bromfenac) UV/Vis	TM058	Pass
Bromfenac Content	TM058	(b) (4) % (b) (4) % of label)
Chromatographic Purity	TM058	(b) (4) Unspecified NMT (b) (4) % Total impurities NMT (b) (4) %
Appearance	TM423	Greenish-yellow to yellow, (b) (4) to translucent liquid
pH	TM601	(b) (4)
Osmolality	TM414	(b) (4) mOsm/Kg
Viscosity	TM424	(b) (4) cps
Benzalkonium Chloride	TM055	(b) (4) %
Particulates	TM425	(b) (4) NMT NMT NMT
Sterility	TM800	Sterile

NMT = not more than

FACILITIES INSPECTIONS:

The facilities supporting manufacturing of drug substance and drug product for BromSite (bromfenac ophthalmic solution) 0.075% , NDA 206911, are assessed to be acceptable as of 2/27/2016.

DRUG SUBSTANCE

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
(b) (4)			API Commerical Mfg.	17	6	0	23

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
(b) (4)		CSN / API Commercial Mfg.	None	VAI – (b) (4) (b) (4)	Approve based on Facility History

DRUG PRODUCT

Facility Name	FEI	Profile Code	Responsibilities	Facility Sub-Score	Process Sub-Score	Product Sub-Score	Overall Initial Facility Risk Assessment
	(b) (4)	SLQ	DP Commercial Mfg., Fill, Label, Package, Test/Release Raw Materials and API Commercial Release Tester	29	25	0	54
		CTL	DP Release Testing and Stability Testing DS/DP Commercial Working Standards	11	5	0	16

Establishment Name	FEI Number	Responsibilities and Profile Codes	Initial Risks Identified	Current Status	Final Recommendation
	(b) (4)	SLQ / DP Commercial Mfg. (Fill, Label, Package), Test/Release Raw Materials, and API Commercial Release Tester	High (Ophthalmic (b) (4) Filling Process that (b) (4)	PAI coverage; VAI (b) (4)	Approve based on Inspection (PAI demonstrated firm capable to manage risk)
		CTL / DP Release and Stability Testing, DS/DP Commercial Working Standards	None	AC	Approve based on Facility History

4. Nonclinical Pharmacology/Toxicology

From the original Clinical Pharmacology Review dated 3/15/2016:

The subject of this New Drug Application is BromSite (ISV-303) for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. BromSite (bromfenac ophthalmic solution) 0.075%, represents a reformulation of previously approved products administered via the same topical ocular route. As 505(b)(2) application, the applicant will rely on the FDA general findings of safety and effectiveness of the listed drug Bromday (bromfenac ophthalmic solution) 0.09%; NDA 21-664).

Nonclinical data submitted to support approval of ISV-303 include comparative ocular distribution, pharmacokinetic and ocular toxicity assessment. Compared to BromDay/Xibrom, administration of ISV-303 resulted in approximately 4-fold higher levels in the sclera, choroid and aqueous humor and approximately 1.4-fold higher levels in the vitreous humor. The increased exposure was not associated with ocular toxicity when rabbits were dosed topically BID with up to 0.18% ISV-303 for 14 days.

The applicant proposed drug substance impurity specifications for stability which exceed those recommended in ICH guidance. The applicant included nonclinical studies to qualify the impurity

specifications. No toxicity was associated with BromSite which had undergone forced degradation and contained specified impurities levels which exceed those proposed.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review dated 2/9/2016:

The systemic exposure to bromfenac was assessed in a subgroup of patients enrolled in Study C-12-303-004 following topical ocular BID dosing of ISV-303. Following bilateral topical ocular twice-daily dosing of ISV-303 (bromfenac ophthalmic solution 0.075%), the plasma concentration of bromfenac ranged from below the limit of quantification (LOQ = 0.20 ng/mL) to 2.42 ng/mL at 30-60 min post-dose.

6. Sterility Assurance

From the OPQ Integrated Quality Assessment Review dated 2/27/2016:

The proposed expiration date is 24 months (based on 24 month stability results). The drug product must remain sterile over the course of the stability study. Stability studies were conducted under long-term (25°C/40% RH) conditions. Sterility testing is performed initially and then annually through 36 months. The registration batch numbers 00313-B, -C, and –D were sterile under long-term conditions up to 12 months. The applicant has provided successful results verifying release and stability sterility testing per USP<71>. AET (per USP<51>) will be performed routinely for post-approval stability testing due to AET failures of multiple dose topical ophthalmic products preserved with benzalkonium chloride.

The applicant states that the first three commercial production batches will be placed on a long-term stability program. Every year thereafter, one production batch will be added to the program.

The applicant has provided sufficient results demonstrating the integrity of the container-closure as a microbial barrier.

The Division of Microbiology Assessment has reviewed NDA 206911 for BromSite (bromfenac ophthalmic solution) 0.075%, and found the microbiology information adequate. From a microbiology perspective, NDA 206911 is recommended for **APPROVAL.**

7. Clinical/Statistical - Efficacy

From the Medical Officer Review dated 3/15/2016:

Study	Title	Study Design	Treatment Groups	Population
C-11-303-003 Phase 3	A randomized double-masked study to compare the ocular safety, tolerability, and efficacy of ISV-303 (0.075% bromfenac in DuraSite) to DuraSite vehicle in cataract surgery subjects	Double-masked, randomized, multi-center, 2-arm	ISV-303 (0.075%) (180) DuraSite Vehicle BID (88) For 16 days (the day prior to surgery, the day of surgery and 14 days post-surgery).	Subjects ≥ 18 y/o who have undergone uncomplicated unilateral cataract surgery
C-12-303-004 Phase 3	A randomized double-masked study to compare the ocular safety, tolerability, and efficacy of ISV-303 (0.075% bromfenac in DuraSite) to DuraSite vehicle in cataract surgery subjects	Double-masked, randomized, multi-center, 2-arm	ISV-303 (0.075%) (174) DuraSite Vehicle BID (94) For 16 days (the day prior to surgery, the day of surgery and 14 days post-surgery).	Subjects ≥ 18 y/o who have undergone uncomplicated unilateral cataract surgery

The protocols for Study C-11-303-003 and C-12-303-004 were identical, with the following exceptions incorporated into Protocol C-12-303-004.

- The primary efficacy endpoint was changed from "the proportion of subjects with anterior chamber cell (ACC) Grade of 0 by Day 15" to "the proportion of subjects with ACC Grade of 0 at Day 15." It is important to note both studies were analyzed the same way; the language was prospectively clarified in this second Phase 3 study protocol.
- In order to assess the systemic exposure to bromfenac, a whole blood sample was collected from a subgroup of about 40 subjects on Days 1 and 15, and the bromfenac levels measured in the resultant plasma.
- A second pain measurement instrument was added by having subjects assess pain levels via the subject diary prior to administration of ISV-303.
- Subjects with a history of diabetic retinopathy were allowed if there was no visual impairment.
- Use of triamcinolone was prohibited within 90 days before surgery and throughout the dosing period.

Primary Efficacy Endpoint (US and EU)

- Proportion of subjects with an ACC grade of 0 at Day 15, was based on the mITT Population; the last observation carried forward (LOCF) was used to impute missing data. The difference between treatment with ISV-303 and Vehicle was tested using the chi-square test.

Secondary Efficacy Endpoint (VAS Pain Assessment)

- Proportion of subjects who achieve a pain score of 0 on the VAS (0 to 100 mm scale) at each postsurgical assessment.

Analysis of Primary Endpoint(s)

Study C-11-303-003: Primary Efficacy Endpoint Results-Proportion of Subjects with an ACC Grade of 0 in the Study Eye at Day 15 (mITT)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
0 (Did not receive rescue therapy)	96 (57.1%)	16 (18.8%)	<0.001
0 (Received rescue therapy)	2 (1.2%)	3 (3.5%)	
>0	70 (41.7%)	66 (77.6%)	

Study C-12-303-004: Primary Efficacy Endpoint Results-Proportion of Subjects with an ACC Grade of 0 in the Study Eye at Day 15 (mITT)

ACC Grade	ISV-303 N=168	Vehicle N=85	Adjusted p-value
0 (Did not receive rescue therapy)	64 (38.1%)	19 (22.4%)	0.035
0 (Received rescue therapy)	0	0	
>0	104 (61.9%)	66 (77.6%)	

Both clinical trials demonstrate statistical significance for the primary efficacy endpoint in the specified mITT population.

Analysis of Secondary Endpoint(s)

Study C-11-303-003: Proportion of Subjects Who Achieved a Pain Score of 0 at Each Post-surgical VAS Assessment

Visit (Study Day) Pain Score of 0 (No rescue therapy)	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1)	129 (76.8%)	41 (48.2%)	<0.001
Visit 4 (Day 8)	152 (90.5%)	33 (38.8%)	<0.001
Visit 5 (Day 15)	156 (92.9%)	37 (42.4%)	<0.001
Visit 6 (Day 29)	143 (85.1%)	40 (47.1%)	<0.001

Study C-12-303-004: Proportion of Subjects Who Achieved a Pain Score of 0 at Each Post-surgical VAS Assessment

Visit (Study Day) Pain Score of 0 (No rescue therapy)	ISV-303 N=168	Vehicle N=85	Adjusted p-value
Visit 3 (Day 1)	138 (82.1%)	53 (62.4%)	<0.001
Visit 4 (Day 8)	145 (86.3%)	43 (50.6%)	<0.001
Visit 5 (Day 15)	146 (86.9%)	49 (57.6%)	<0.001
Visit 6 (Day 29)	140 (83.3%)	51 (60.0%)	<0.001

Both clinical trials demonstrate statistical significance in the proportion of subjects who achieved a pain score of 0 at each postsurgical VAS assessment. Analysis of the secondary efficacy endpoint was based on the mITT Population; the LOCF method was used to impute missing data.

Efficacy Summary Statement

Two adequate and well controlled studies demonstrate the efficacy of BromSite (bromfenac ophthalmic solution) 0.075% for treatment of post-operative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

8. Safety

From the Medical Officer Review dated 3/15/2016:

Two clinical studies (C-11-303-003 and C-12-303-004) were used to evaluate safety. Study C-10-303-001 was not be used to support efficacy because it only started dosing post-surgery not pre-surgery as in Studies C-11-303-003 and C-12-303-004.

Common Adverse Events

Study C-11-303-003: Summary of All Treatment Emergent AEs by System Organ Class (Safety Population)

	ISV-303 N=169	Vehicle N=85
Number of Treatment Emergent AEs	90	53
Number of Subjects with TEAEs	52	37
Cardiac Disorders		
Coronary artery occlusion	1	0
Eye disorders		
Blepharitis	1	0
Ciliary hyperemia	1	0
Conjunctival hyperemia	0	1
Corneal edema	2	0
Corneal opacity	0	1
Corneal striae	0	1
CME	1	1
Diplopia	1	0
Dry eye	1	0
Eye inflammation	0	2
Eye pain	8	11
Foreign body sensation	3	1
Iritis	3	5
Lacrimation increased	1	1
Meibomian gland dysfunction	1	0
Ocular discomfort	2	3
Ocular hyperemia	0	1

Ocular hypertension	16	3
Photophobia	1	4
Posterior capsular rupture	1	0
Retinal hemorrhage	0	1
Retinal tear	1	0
Trichiasis	1	0
Uveitis	1	0
Visual impairment	1	0
Vitreous floaters	4	0
GI disorders		
Abdominal distention	1	0
Abdominal pain upper	1	0
Diarrhea	1	0
Nausea	1	2
General Disorders		
Chest pain	1	0
Instillation site pain	2	1
Pain	0	1
Infections		
Bronchitis	0	1
Endopthalmitis	0	1
Influenza	1	0
Sinusitis	1	0
Upper respiratory tract infection	1	1
Injury		
Corneal abrasion	1	0
Incision site complication	0	1
Ligament sprain	1	0
Spinal compression fracture	1	0
Investigations		
Pancreatic enzymes increased	1	0
Metabolism disorders		
Gout	0	1
Musculoskeletal disorders		
Arthralgia	1	0
Musculoskeletal stiffness	1	0
Nervous system disorders		
HA	4	5
Psychiatric disorders		
Bipolar disorders	1	0
Depression	1	0
Panic attack	1	0

Respiratory disorders		
Cough	1	0
Epistaxis	1	0
Nasal congestion	1	0
Pleurisy	1	0
Skin disorders		
Pruritis	1	0
Pruritis generalized	1	0
Rash	1	0
Rosacea	1	0
Skin wrinkling	1	0
Vascular disorders		
Hyperemia	1	3
HTN	2	0

Study C-12-303-004: Summary of All Treatment Emergent AEs by System Organ Class (Safety Population)

	ISV-303 N=170	Vehicle N=85
Number of Subjects with TEAEs	49	25
Cardiac Disorders		
Bradycardia	1	0
Congenital and genetic disorders		
Corneal dystrophy	1	0
Eye disorders		
AC cell	1	0
AC inflammation	5	3
Conjunctival hemorrhage	3	0
Conjunctival hyperemia	0	1
Corneal deposits	1	0
Corneal disorder	0	1
Corneal edema	1	1
Cystoid macular edema	1	1
Deposit eye	1	0
Dry eye	0	1
Eye irritation	1	1
Eye pain	4	2
Eyelid margin crusting	1	0
Eyelid ptosis	0	1
Foreign body sensation	0	1
Iritis	5	2
Lens dislocation	1	0
Ocular hyperemia	1	1
Ocular hypertension	17	5
Photopsia	1	0
Punctate keratitis	3	1
Retinal hemorrhage	1	0
Retinal vein occlusion	1	0

Vision blurred	1	1
Visual acuity reduced	0	1
Vitreous adhesions	1	0
Vitreous detachment	0	1
Vitreous loss	1	0
GI disorders		
Colitis	0	1
Dyspepsia	0	1
Nausea	1	0
Vomiting	1	0
General disorders		
Chest pain	1	0
Pain	0	1
Immune System disorders		
Drug hypersensitivity	1	0
Infections		
Nasophharyngitis	1	0
Sepsis	0	1
Sinusitis	1	0
UTI	0	1
Injury		
Corneal abrasion	0	1
Foreign body in eye	3	1
Post-procedureal discomfort	1	0
Posterior capsule opacification	2	1
Metabolism disorders		
Dehydration	0	1
Hyperglycemia	1	0
Hyperkalemia	1	1
Neoplasms		
Dizziness	2	0
HA	1	0
Migraine with aura	0	1
Renal disorders		
Renal failure acute	0	
Respiratory disorders		
Dysopnea	1	0
Upper respiratory tract congestion	1	0
Skin disorders		
Dermatitis contact	1	0
Hyperhidrosis	1	0
Rash	1	0

Table 2.7.4-7: Summary of Common (≥ 1%) Treatment-Emergent Adverse Events (Integrated Safety Population)

SOC Preferred Term	Treatment Group		
	ISV-303 (N = 422) n (%)	Xibrom (N = 42) n (%)	Vehicle (N = 212) n (%)
Subjects with at least 1 TEAE	123 (29.1)	9 (21.4)	72 (34.0)
Subjects with at least one common TEAE	78 (18.5)	9 (21.4)	51 (24.1)
Eye Disorders	68 (16.1)	4 (9.5)	43 (20.3)
Anterior Chamber Inflammation	5 (1.2)	0	3 (1.4)
Eye Inflammation	3 (0.7)	1 (2.4)	4 (1.9)
Eye Pain	13 (3.1)	0	14 (6.6)
Eye Pruritus	2 (0.5)	1 (2.4)	0
Foreign Body Sensation in Eyes	3 (0.7)	2 (4.8)	2 (0.9)
Iritis	12 (2.8)	1 (2.4)	8 (3.8)
Ocular Discomfort	2 (0.5)	0	3 (1.4)
Ocular Hypertension	34 (8.1)	0	8 (3.8)
Photophobia	1 (0.2)	0	4 (1.9)
Visual Acuity Reduced	0	0	3 (1.4)
Vitreous Floaters	6 (1.4)	0	1 (0.5)
Injury, Poison, Procedural Complication	4 (0.9)	1 (2.4)	1 (0.5)
Foreign Body in Eye	4 (0.9)	1 (2.4)	1 (0.5)
Nervous System Disorders	5 (1.2)	1 (2.4)	6 (2.8)
Headache	5 (1.2)	1 (2.4)	6 (2.8)
Respiratory, Thoracic, Mediastinal Disorders	1 (0.2)	2 (4.8)	0
Chronic Obstructive Pulmonary Disease	0	1 (2.4)	0
Epistaxis	1 (0.2)	1 (2.4)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	2 (0.5)	1 (2.4)	0 (0.0)
Rash	2 (0.5)	1 (2.4)	0 (0.0)
Vascular Disorders	1 (0.2)	0	3 (1.4)
Hyperaemia	1 (0.2)	0	3 (1.4)

SOC = system organ class; TEAE = treatment-emergent adverse event
Source: Tables 3.1.2 and 3.1.3.

The most commonly reported adverse events following use of BromSite after cataract surgery include: anterior chamber inflammation (iritis), headache, vitreous floaters, eye pain and elevated intraocular pressure (ocular hypertension). These reactions were reported in roughly 1.2% to 8.1 % of patients.

Nonfatal Serious Adverse Events

Study C-11-303-003: SAEs

Subject	Group	Description
105-022	Vehicle	The SAE of endophthalmitis began 4 days after surgery, and the subject was withdrawn from the study at that point. The same day treatment was initiated with prednisolone (1 drop, hourly), ketorolac (QID), homatropine (TID), vancomycin (q2h), moxifloxacin (400 mg po QD), vancomycin (1 mg single ocular injection), and ceftazidime (2.25 mg single ocular injection); difluprednate (q2h) was added 10 days subsequent to withdrawal. The SAE was indicated to have resolved after 38 days.

Study C-12-303-004: SAEs

Subject	Group	Description
264-009	ISV-303	A 71 yo Caucasian male whose first dose of study drug was administered on (b) (6) and was stopped on His cataract surgery took place on (b) (6). An episode of severe chest pain occurred the same day as surgery and resolved on (b) (6) with no action taken.
316-004	Vehicle	A 77 yo Caucasian female whose first dose of study drug was administered on (b) (6) and stopped on (b) (6) Cataract surgery took place on (b) (6). An episode of colitis of moderate intensity started on (b) (6) and the subject was hospitalized, but not withdrawn from the study. The colitis resolved on (b) (6).

These types of adverse events are consistent with the age of the population of enrolled patients, and they do not appear directly attributable to the drug product. Two of the three events are related to use of vehicle.

Deaths

There were no deaths reported in Study C-11-303-003 and C-12-303-004.

Overall Exposure at Appropriate Doses/Durations

Study C-11-303-003: Exposure to Study Drug: Study Eye by Treatment Group (Safety Population)

Exposure	ISV-303 N=169	Vehicle N=85
Subjects exposed to study drug	169	85
Subjects completed all doses	135	66
Exposure (doses)		
N	168	84
Mean (sd)	30.0 (6.3)	21.4 (10.3)
Min, Max	1, 39	2, 34

Study C-12-303-004: Exposure to Study Drug: Study Eye by Treatment Group (Safety Population)

Exposure	ISV-303 N=170	Vehicle N=85
Subjects exposed to study drug	170	85
Subjects completed all doses	140	75
Exposure (doses)		
N	166	85
Mean (sd)	29.5 (7.4)	25.1 (9.2)
Min, Max	2, 34	4, 35

Safety Summary Statement

Two adequate and well controlled studies demonstrate the safety of BromSite (bromfenac ophthalmic solution) 0.075% for treatment of post-operative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

The most commonly reported adverse events following use of BromSite after cataract surgery include: anterior chamber inflammation (iritis), headache, vitreous floaters, eye pain and ocular hypertension. These reactions were reported in roughly 1% to 8% of patients.

9. Advisory Committee Meeting

There were no issues raised during the review of this application that were believed to benefit from discussion at an Advisory Committee meeting.

10. Pediatrics

Safety and effectiveness of BromSite in pediatric patients below the age of 18 years has not been established. During the pre-NDA meeting, the Agency recommend that InSite submit a Pediatric Study Plan (PSP). The Applicant did not submit a PSP but in the NDA submission did request a full waiver with the following justification:

> InSite Vision believes that the number of pediatric patients under 18 years with cataracts requiring surgery, in the US, is so small that it is impractical to study this population, and that ISV-303 is not likely to provide a meaningful therapeutic benefit over existing therapies (i.e., corticosteroids) for those few pediatric patients who do undergo cataract surgery since corticosteroid use is the standard of care in this population.

This application did not trigger PREA and was not presented at PERC.

11. Other Relevant Regulatory Issues

OSI
An Office of Scientific Investigations (OSI) audit was requested.

The studies, "C-11-303-003 and C-12-303-004 entitled, "A Randomized Double-masked Study to Compare the Ocular Safety, Tolerability, and Efficacy of ISV-303 (0.075% bromfenac in Durasite) to Durasite Vehicle in Cataract Surgery Subjects," were inspected in support of this application. The sites of Drs. Berdy, Walters, DaVanzo, and McLaurin were chosen because of their relatively large enrollment numbers.

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Gregg Jonathan Berdy, M.D. Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	C-11-303-003/ 105/ 22	9-10 Sep 2015	NAI
Thomas R. Walters, M.D. Texan Eye, PA / Keystone Research, Ltd. 5717 Balcones Drive Austin, TX 78731	C-11-303-003/ 6/ 30	30 Oct-3 Nov 2015	NAI
Robert J. DaVanzo, M.D. Cornerstone Health Care 307 North Lindsay Street High Point, NC 27262	C-12-303-004/ 321/ 34	27 Jul-3 Aug 2015	NAI
Eugene B. McLaurin, M.D. Total Eye Care, P.A. 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	C-12-303-004/ 264/ 21	21-23 Sep 2015	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

None of these sites were issued a Form FDA 483.The final classification of each of these inspections was No Action Indicated (NAI). The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

FINANCIAL DISCLOSURE
The applicant has examined its financial data regarding significant payments of other sorts made to all investigators in the studies and equity information as provided by the investigators, as defined in 21 CFR 54.2. There were no disclosed financial interests/arrangements. There is no evidence to suggest that the results of the study were impacted by any financial payments.

DIVISION OF MEDICATION ERROR PREVENTION AND ANALYSIS (DMEPA)
In a review finalized 9/14/2015, DMEPA has reviewed the proposed carton labeling, bottle label and prescribing information. DMEPA provided recommendations on the packaging configuration and the package insert labeling. These are incorporated into the Medical Officer's labeling where appropriate.

DMEPA concluded that the proposed proprietary name, Bromsite, was conditionally acceptable in a letter to the applicant dated 10/15/2015.

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)
In a review finalized 3/1/2016, OPDP has reviewed the proposed product labeling (i.e., package insert). These are incorporated into the Medical Officer's labeling where appropriate.

DIVISION OF MEDICAL POLICY PROGRAMS (DMPP)
In a review finalized 3/4/2016, DMPP has reviewed the proposed Instructions for Use. DMPP provided track changes and clean versions of the revised Instructions for Use. Two sentences, (b) (4) were deleted from the DMPP revision since this information was also removed from the package insert labeling.

BIOSTATISTICS
Per the Biostatistics consultative review finalized 2/9/2016:

The NDA included the efficacy and safety results from two identically designed clinical trials, Studies C-11-303-003 and C-12-303-004 (also referred to as Study 003 and Study 004 throughout this review). Both Studies 003 and 004 were prospective, multicenter, randomized, double-masked, vehicle-controlled, parallel-group studies. For both studies, the primary efficacy endpoint was the proportion of subjects with anterior chamber cell (ACC) grade of 0 without rescue therapy by Day 15; and the secondary endpoint was the proportion of subjects with a pain grade of 0 without rescue therapy in the study eye at each post-surgical visit (Days 1, 8, 15, and 29). The primary analysis set for the evaluation of the primary and secondary efficacy endpoints was the modified intent-to-treat (mITT) population, which included all subjects who were randomized, underwent cataract surgery, and received at least one dose of study treatment.

For Study 003, at Day 15 visit, 57.1% (96/168) of the patients in the ISV-303 group had an ACC grade of 0 without rescue therapy compared with 18.8% (16/85) of the patients in the Vehicle group; the treatment difference 38.3% was statistically significant ($p<0.001$) with a 95% CI of (27.1%, 49.5%). For Study 004, at the Day 15 visit, 38.1% (64/168) of the patients in the ISV- 303 group had an ACC grade of 0 without rescue therapy compared with 22.4% (19/85) of the patients in the Vehicle group; the treatment difference 15.7% was statistically significant ($p=0.035$) with a 95% CI of (4.2%, 27.3%). In Study 003, at each of the postsurgical visits (Days 1, 8, 15, and 29), proportionally more ISV-303-treated subjects (76.8%, 90.5%, 92.9% and 85.1%, respectively) had no pain (VAS score of 0 without rescue therapy), compared with vehicle-treated subjects (48.2%, 38.8%, 42.4% and 47.1%, respectively), and the differences in proportions (28.6%, 51.7%, 50.5%, and 38.1%, respectively) were statistically significant ($p < 0.001$) with 95% CI of (16.2%, 40.9%), (40.4%, 62.9%), (39.3%, 61.7%), and (26.2%, 50.0%), respectively. In Study 004, proportionally more

ISV-303-treated subjects (82.1%, 86.3%, 86.9% and 83.3%, respectively) were pain free (VAS score of 0 without rescue therapy) compared with vehicle-treated subjects (62.4%, 50.6%, 57.6% and 60.0%, respectively). The differences in proportions (19.8%, 35.7%, 29.3%, and 23.3%, respectively) were statistically significant ($p < 0.001$) with 95% CI of (8.0%, 31.6%), (23.9%, 47.6%), (17.6%, 40.9%), and (11.5%, 35.2%), respectively.

12. Labeling

NDA 206911, BromSite (bromfenac ophthalmic solution) 0.075%, is recommended for approval for treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery with the labeling submitted 4/7/2016 found in the Appendix at the end of this CDTL review.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
NDA 206911, BromSite (bromfenac ophthalmic solution) 0.075%, is recommended for approval for treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

The most commonly reported adverse events following use of BromSite after cataract surgery include: anterior chamber inflammation (iritis), headache, vitreous floaters, eye pain and ocular hypertension. These reactions were reported in roughly 1% to 8% of patients.

RISK BENEFIT ASSESSMENT:
The benefits of using this drug product outweigh the risks for the above indication.

Pharmacology/Toxicology, CMC, Biostatistics, Clinical, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.

Appendix

NDA 206911, BromSite (bromfenac ophthalmic solution) 0.075%, is recommended for approval for treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery with the labeling submitted on 4/7/2016.

11 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 and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
04/08/2016

WILEY A CHAMBERS
04/08/2016