BROMFENAC- bromfenac sodium solution/ drops
Mylan Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use bromfenac ophthalmic solution 0.09% safely and effectively. See full prescribing information for bromfenac ophthalmic solution 0.09%.

BROMFENAC ophthalmic solution 0.09%
Initial U.S. Approval: 1997

INDICATIONS AND USAGE

Bromfenac ophthalmic solution is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction **(1)**.

DOSAGE AND ADMINISTRATION

One drop should be applied to the affected eye two times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period **(2.1)**.

DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution: bromfenac 0.09% **(3)**

CONTRAINDICATIONS

None **(4).**

WARNINGS AND PRECAUTIONS

- Sulfite Allergic Reactions **(5.1)**
- Slow or Delayed Healing **(5.2)**
- Potential for cross-sensitivity **(5.3)**
- Increase bleeding of ocular tissues **(5.4)**
- Corneal effects including keratitis **(5.5)**
- Contact Lens Wear **(5.6)**

ADVERSE REACTIONS

The most commonly reported adverse reactions in 2% to 7% of patients were abnormal sensation in eye, conjunctival hyperemia and eye irritation (including burning/stinging) **(6.1)**.

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch* or Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Bromfenac ophthalmic solution 0.09% is indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

One drop of bromfenac ophthalmic solution should be applied to the affected eye two times daily beginning 24 hours after cataract surgery and continuing through the first 2 weeks of the postoperative period.

2.2 Use with Other Topical Ophthalmic Medications

Bromfenac ophthalmic solution may be administered in conjunction with other topical ophthalmic medications such as alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, cycloplegics, and mydriatics. Drops should be administered at least 5 minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Topical ophthalmic solution: bromfenac 0.09%.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Sulfite Allergic Reactions

Contains sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

5.2 Slow or Delayed Healing

All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

5.3 Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

5.4 Increased Bleeding Time

With some NSAIDs, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularly applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

It is recommended that bromfenac ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

5.5 Keratitis and Corneal Reactions

Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.

Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Post-marketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for the occurrence and severity of corneal adverse events.

5.6 Contact Lens Wear

Bromfenac ophthalmic solution should not be administered while wearing contact lenses. Remove contact lenses prior to instillation of bromfenac ophthalmic solution. The preservative in bromfenac ophthalmic solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of bromfenac ophthalmic solution.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions reported following use of bromfenac after cataract surgery include: abnormal sensation in eye, conjunctival hyperemia, eye irritation (including burning/stinging), eye pain, eye pruritus, eye redness, headache, and iritis. These reactions were reported in 2% to 7% of patients.

6.2 Post-Marketing Experience

The following reactions have been identified during post-marketing use of bromfenac ophthalmic solution 0.09% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical bromfenac ophthalmic solution 0.09% or a combination of these factors, include corneal erosion, corneal perforation, corneal thinning, and epithelial breakdown *[see Warnings and Precautions (5.5)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies with bromfenac ophthalmic solution in pregnant women. No malformations were observed in reproduction studies in rats and rabbits with oral doses of bromfenac at exposures up to 150 times (rats) and 90 times (rabbits) the predicted human systemic exposure; however, both embryolethality and maternal toxicity were observed at the highest dose exposures. The systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans, following ocular administration *[see Clinical Pharmacology (12.3)]*. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Premature closure of the ductus arteriosus in the fetus has occurred with third trimester use of oral and injectable NSAIDs. Measurable maternal and fetal plasma drug levels are available with oral and injectable routes of NSAID administration. The maternal plasma level of bromfenac ophthalmic solution following ocular administration is unknown *[see Clinical Pharmacology (12.3)]*.

Animal Data

Reproduction studies performed in rats at oral doses of bromfenac up to 0.9 mg/kg/day (systemic exposure 90 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and rabbits at oral doses up to 7.5 mg/kg/day (150 times the predicted human systemic exposure) produced no drug-related malformations in reproduction studies. However, embryo-fetal lethality and maternal toxicity were produced in rats and rabbits at 0.9 mg/kg/day and 7.5 mg/kg/day, respectively. In rats, bromfenac treatment caused delayed parturition at 0.3 mg/kg/day (30 times the predicted human exposure), and caused dystocia, increased neonatal mortality and reduced postnatal growth at 0.9 mg/kg/day.

8.3 Nursing Mothers

It is not known if bromfenac ophthalmic solution is present in human milk. The systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans,

following ocular administration *[see Clinical Pharmacology (12.3)]*. Based on the low level of systemic exposure, it is unlikely that bromfenac ophthalmic solution would be detected in human milk using available assays. Caution should be exercised when bromfenac ophthalmic solution is administered to a nursing woman.

8.4 Pediatric Use

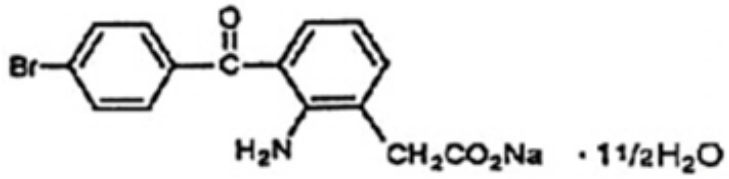
Safety and efficacy in pediatric patients below the age of 18 have not been established.

8.5 Geriatric Use

There is no evidence that the efficacy or safety profiles for bromfenac ophthalmic solution differ in patients 65 years of age and older compared to younger adult patients.

11 DESCRIPTION

Bromfenac ophthalmic solution 0.09% is a sterile, topical, nonsteroidal anti-inflammatory drug (NSAID) for ophthalmic use. Each mL of bromfenac ophthalmic solution contains 1.035 mg bromfenac sodium sesquihydrate (equivalent to 0.9 mg bromfenac free acid). Bromfenac sodium is designated chemically as sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, with an molecular formula of $C_{15}H_{11}BrNNaO_3 \cdot 1½H_2O$. The structural structure for bromfenac sodium is:



Bromfenac sodium is a yellow to orange crystalline powder. The molecular weight of bromfenac sodium is 383.17. Bromfenac ophthalmic solution is supplied as a sterile aqueous 0.09% solution, with a pH of 8.3. The osmolality of bromfenac ophthalmic solution is approximately 300 mOsmol/kg.

Each mL of bromfenac ophthalmic solution contains:

Active: bromfenac sodium sesquihydrate 0.1035% equivalent to 0.9 mg bromfenac free acid

Preservative: benzalkonium chloride (0.05 mg/mL)

Inactives: boric acid, disodium edetate (0.2 mg/mL), polysorbate 80 (1.5 mg/mL), povidone (20 mg/mL), sodium borate, sodium sulfite anhydrous (2 mg/mL), sodium hydroxide to adjust pH and water for injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of its action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2.

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

12.3 Pharmacokinetics

The plasma concentration of bromfenac following ocular administration of bromfenac ophthalmic solution 0.09% in humans is unknown. Based on the maximum proposed dose of one drop to the eye (0.09 mg) twice a day and PK information from other routes of administration, the systemic concentration of bromfenac is estimated to be below the limit of quantification (50 ng/mL) at steady-state in humans.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats and mice given oral doses of bromfenac up to 0.6 mg/kg/day (systemic exposure 30 times the systemic exposure predicted from the recommended human ophthalmic dose [RHOD] assuming the human systemic concentration is at the limit of quantification) and 5 mg/kg/day (340 times the predicted human systemic exposure), respectively revealed no significant increases in tumor incidence. Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Bromfenac did not impair fertility when administered orally to male and female rats at doses up to 0.9 mg/kg/day and 0.3 mg/kg/day, respectively (systemic exposure 90 and 30 times the predicted human exposure, respectively).

14 CLINICAL STUDIES

14.1 Ocular Inflammation and Pain

Clinical efficacy was evaluated in two randomized, double-masked, vehicle-controlled U.S. trials in which subjects with a summed ocular inflammation score ≥3 after cataract surgery were assigned to bromfenac ophthalmic solution or vehicle in a 2:1 ratio following surgery. One drop of bromfenac ophthalmic solution or vehicle was self-instilled in the study eye twice a day for 14 days, beginning the day after surgery. The primary endpoint was reduction of ocular inflammation (to trace inflammation or clearing) assessed 14 days post-surgery using a slit lamp binocular microscope. In the intent-to-treat analyses of both studies a significant effect of bromfenac ophthalmic solution on ocular inflammation after cataract surgery was demonstrated (62% to 66% vs. 40% to 48%).

An additional efficacy end point was the time required for resolution of ocular pain in subjects who reported pain. Overall, only 20% of the patients undergoing cataract surgery in these trials had pain on the first day after surgery. In these patients, the bromfenac ophthalmic solution group demonstrated a statistically significant difference in median time to resolution of ocular pain of 2 days compared to 4 days for patients receiving vehicle.

16 HOW SUPPLIED/STORAGE AND HANDLING

Bromfenac ophthalmic solution 0.09% is supplied in a white LDPE plastic squeeze bottle with a 15 mm LDPE white dropper-tip and 15 mm polypropylene gray cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

NDC 0378-7109-35
5 mL in 10 mL container

NDC 0378-7110-35
2.5 mL in 6 mL container

STORAGE

Store at 20º to 25°C (68º to 77°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

17.1 Slowed or Delayed Healing

Advise patients of the possibility that slow or delayed healing may occur while using NSAIDs.

17.2 Sterility of Dropper Tip

Advise patients to not touch dropper tip to any surface, as this may contaminate the contents.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

17.3 Concomitant Use of Contact Lenses

Advise patients that contact lenses should not be worn during the use of this product. The preservative in bromfenac ophthalmic solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of bromfenac ophthalmic solution.

17.4 Concomitant Topical Ocular Therapy

Advise patients that if more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart.

Distributed by:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

013063
REVISED FEBRUARY 2014
CL:BROM:R3

PRINCIPAL DISPLAY PANEL - 5 mL Bottle Carton

NDC 0378-**7109**-35
5 mL

Twice Daily

Bromfenac Ophthalmic
Solution 0.09%

For topical application in the eye

Mylan®

Rx only
Sterile

PRINCIPAL DISPLAY PANEL - 2.5 mL Bottle Carton

NDC 0378-**7110**-35
2.5 mL

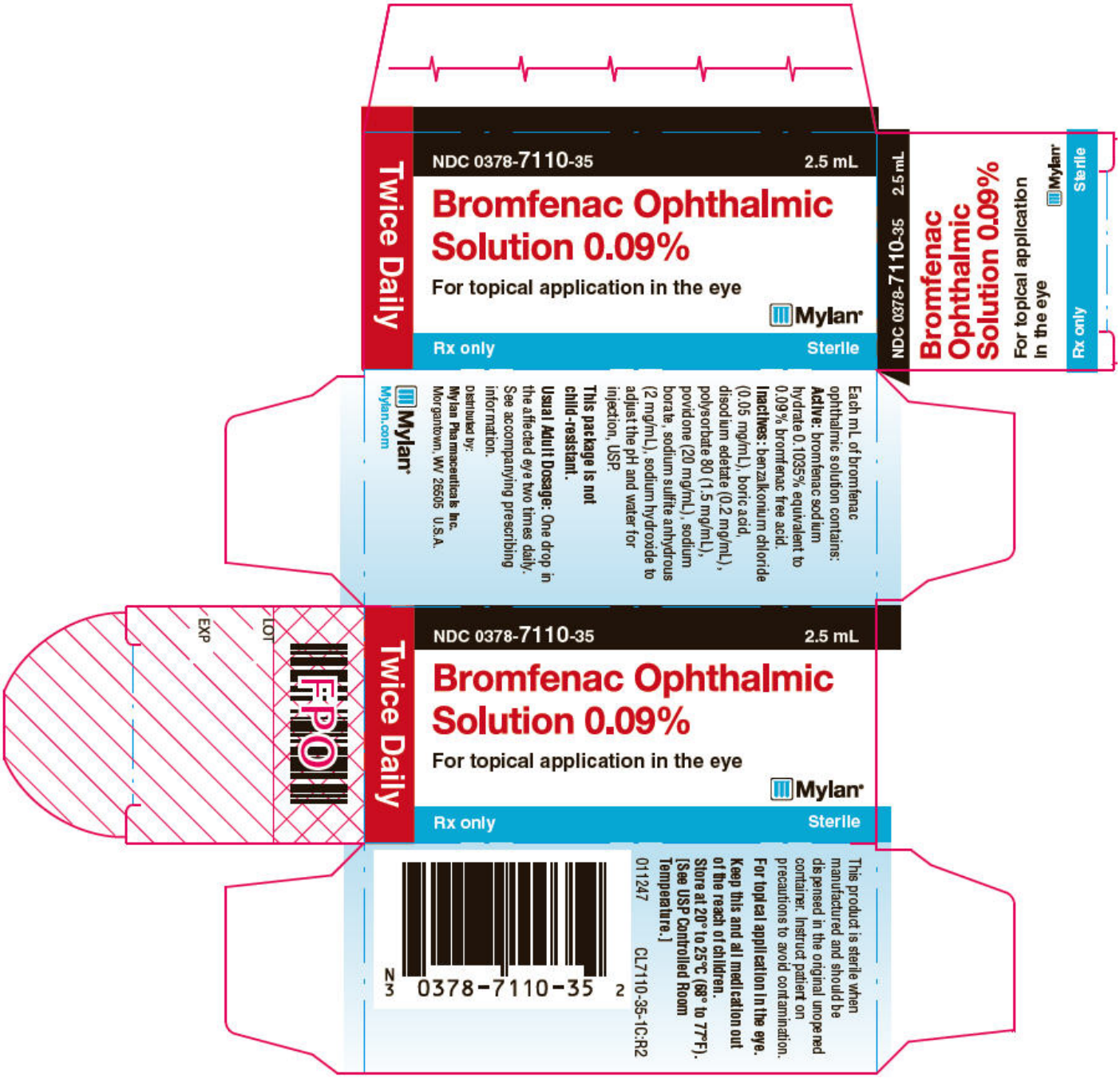
Twice Daily

Bromfenac Ophthalmic
Solution 0.09%

For topical application in the eye

Mylan®

Rx only
Sterile



PRINCIPAL DISPLAY PANEL - 2.5 mL Sample Bottle Carton

NDC 0378-**7111**-35
2.5 mL

Twice Daily

Bromfenac Ophthalmic Solution 0.09%

For topical
application in the eye

PROFESSIONAL SAMPLE
NOT TO BE SOLD

Mylan®

Rx only
Sterile

BROMFENAC

bromfenac sodium solution/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-7110
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Bromfenac sodium (UNII: 8ECV571Y37) (Bromfenac - UNII:864P0921DW)	Bromfenac	0.9 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
Benzalkonium chloride (UNII: F5UM2KM3W7)	0.05 mg in 1 mL
Boric acid (UNII: R57ZHV85D4)	11 mg in 1 mL
edetate disodium (UNII: 7FLD91C86K)	0.2 mg in 1 mL
polysorbate 80 (UNII: 6OZP39ZG8H)	1.5 mg in 1 mL
povidones (UNII: FZ989GH94E)	20 mg in 1 mL
sodium borate (UNII: 91MBZ8H3QO)	11 mg in 1 mL
sodium sulfite (UNII: VTK01UQK3G)	2 mg in 1 mL
sodium hydroxide (UNII: 55X04QC32I)	
water (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0378-7110-35	1 in 1 CARTON		
1		2.5 mL in 1 BOTTLE, DROPPER		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201211	05/11/2011	

BROMFENAC

bromfenac sodium solution/ drops

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-7109
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
Bromfenac sodium (UNII: 8ECV571Y37) (Bromfenac - UNII:864P0921DW)	Bromfenac	0.9 mg in 1 mL

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povidones (UNII: FZ989GH94E)	20 mg in 1 mL
sodium borate (UNII: 91MBZ8H3QO)	11 mg in 1 mL
sodium sulfite (UNII: VTK01UQK3G)	2 mg in 1 mL
sodium hydroxide (UNII: 55X04QC32I)	
water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-7109-35	1 in 1 CARTON		
1		5 mL in 1 BOTTLE, DROPPER		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201211	05/11/2011	

BROMFENAC

bromfenac sodium solution/ drops

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0378-7111
Route of Administration	OPHTHALMIC		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Bromfenac sodium (UNII: 8ECV571Y37) (Bromfenac - UNII:864P0921DW)	Bromfenac	0.9 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Benzalkonium chloride (UNII: F5UM2KM3W7)	0.05 mg in 1 mL
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povidones (UNII: FZ989GH94E)	20 mg in 1 mL
sodium borate (UNII: 91MBZ8H3QO)	11 mg in 1 mL
sodium sulfite (UNII: VTK01UQK3G)	2 mg in 1 mL
sodium hydroxide (UNII: 55X04QC32I)	
water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0378-7111-35	1 in 1 CARTON		
1		2.5 mL in 1 BOTTLE, DROPPER		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA201211	05/11/2011	

Labeler - Mylan Pharmaceuticals, Inc. (059295980)

Establishment

Name	Address	ID/FEI	Business Operations
Patheon Manufacturing Services LLC		079415560	Manufacture(0378-7110, 0378-7109, 0378-7111)

Revised: 5/2014 Mylan Pharmaceuticals, Inc.