URGENT: DRUG RECALL – OPHTHALMIC SOLUTION DOSAGE FORM

Date: May 7, 2025

Alembic Pharmaceuticals Limited (Formulation Division-III),
Village - Karakhadi, Taluka – Padra,
Vadodara – 391450,
Gujarat, India.

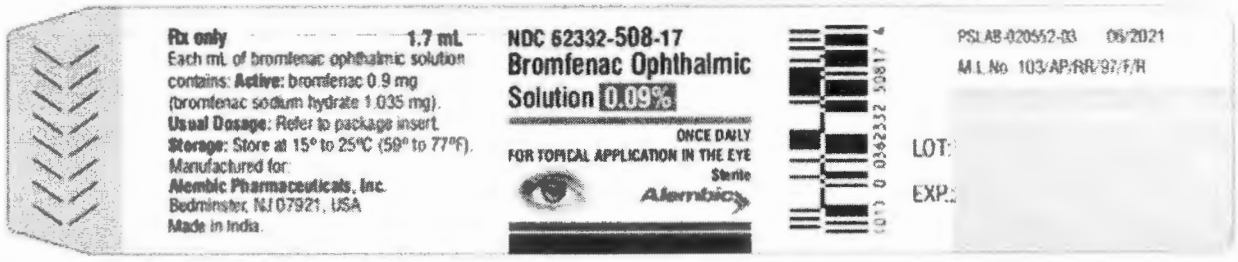
Dear Distributor, Retailer,

This is to inform you of a product recall involving 3 lots of Bromfenac Ophthalmic Solution 0.09%:

RE: Bromfenac Ophthalmic Solution 0.09%, NDC number: 62332-508-17, Lots No. 7230309, 7230310, 7230311, All 3 Lots have Exp. Date: May 31, 2025.

See enclosed product label for ease in identifying the product at the retail level.

Product Label:



This recall has been initiated due to the product (Bromfenac ophthalmic solution 0.09%) being out of specification at the time of testing i.e. 18th month stability testing. This recall is precautionary to remove any out of specification product from the market.

ALEMBIC PHARMACEUTICALS LIMITED
ALEMBIC ROAD, VADODARA - 390 003. • TEL : (0265) 2280550, 2280880 • FAX : (0265) 2282506
Website: www.alembicpharmaceuticals.com
SITE ADDRESS : ***ALEMBIC PHARMACEUTICALS LIMITED*** (FORMULATION DIVISION-III, KARAKHADI)
FACTORY : SURVEY NO. 779/790, KARAKHADI, TAL. PADRA, DIST. VADODARA, PIN-391450, GUJARAT.
CIN No. : L24230GJ2010PLC061123, **PAN No. :** AAICA5591M

There have been no known reported adverse events associated product change and the recall is limited to the 3 identified lots.

Please examine your stocks immediately to determine if you have any of the units of Lots 7230309, 7230310 and 7230311 on hand. Any distributors or retailers that received this product should discontinue dispensing (distributing) the lot and promptly return via parcel post to Inmar Rx Solutions, 3845 Grand Lakes Way, Suite 125, Grand Prairie, TX 75050. This Recall should be performed to the retail level only.

If you have stock available, please discontinue dispensing (distributing) the lot 7230309, 7230310 and 7230311 and promptly complete and return the enclosed stock response form as soon as possible. Above mentioned lots of product were distributed between 10/19/2023 to 5/29/2024.

Your assistance is appreciated and necessary to prevent further distribution.

Retailers with questions regarding this recall can contact Alembic Pharmaceuticals Inc by phone at +1 908-552-5839 (9am – 5pm EDT, Monday through Friday) or email address david.cobb@alembicusa.com

This recall is being made with the knowledge of the US Food and Drug Administration.

We appreciate your assistance in this matter.

Nitin Lanjewar,

Head –Quality Assurance

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CIN No. : L24230GJ2010PLC061123, **PAN No. :** AAICA5591M

STOCK RESPONSE FORM

Recall of Bromfenac Ophthalmic Solution 0.09%
Lots 7230309, 7230310, 7230311
Retail Level
(05/06/2025)

Please fill out this form completely. By doing so, this will acknowledge that you have read and understand the recall instructions and have taken the appropriate action.

Customer Name _____ DEA #_____

**DEA # is required, if it is not provided, the processing of your form will be delayed.*

Address_____

City_____ State_____ Zip_____

Contact Name (please print)_____ Telephone #_____

Contact Signature _____ Date_____

I have checked my stock and:

_____Do not have any stock of the **recall product**.

OR

I have quarantined and listed in the box below the quantity of recall units and I will be returning to Inmar, as soon as possible. Upon receipt of this Response Form, Inmar, will issue return authorization label(s) Please indicate the # of needed box labels _____.

Item Description	NDC	Lot #	Qty returning
Bromfenac Ophthalmic Solution 0.09%	**62332-0508-17**	7230309	
Bromfenac Ophthalmic Solution 0.09%	**62332-0508-17**	7230310	
Bromfenac Ophthalmic Solution 0.09%	**62332-0508-17**	7230311	

If you did not purchase the product directly from the Manufacturer, please complete the below section.

Purchased From: Wholesaler Name _____ DEA #_____

City_____ State_____

If you have any questions regarding this form or product return please contact Inmar at 1-800-967-5952. Office hours 9am to 5pm EST Mon thru Fri.

Please fax this form to: 1-817-868-5362 or E-mail rxrecalls@inmar.com

Attachment B-Pharmaceutical

Re: Your Voluntary Recall

This form is intended to obtain **more information** concerning your firm's Voluntary Recall Action Plan.

Please provide detailed information regarding the recall **(please follow the number format below, and do NOT use phrases such as "see attached" or "refer to," instead, please describe it in detail)**:

DO NOT MODIFY OR DELETE ANY QUESTION(S) OR PART THEREOF. ANSWER EACH QUESTION AS IS.

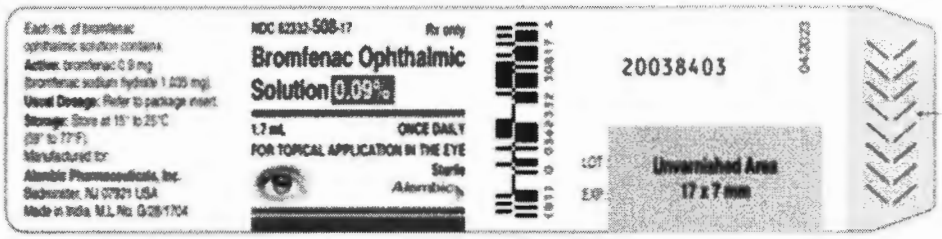
Awareness Date: April 4, 2025

1. PRODUCT(S):
   a. Name: Bromfenac Ophthalmic solution 0.09% (1.7 mL)
   b. Brand Name: Bromfenac Ophthalmic solution 0.09% (1.7 mL)
   c. NDC#/UPC#: 62332-508-17
   d. Type or form (tablets, capsule, liquid, etc.): Sterile ophthalmic solution
   e. Strength per dose, dosage: 0.9mg/ml, Instill one drop into the affected eye once daily.
   f. State: Rx or OTC or Dietary Supplement: Rx
   g. Provide Product Indication (A brief description of the product and its use.): Bromfenac ophthalmic solution 0.09% 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.
   h. Date(s) of Manufacture. **Please give both the beginning and ending dates** (e.g. 12/15/00 to 03/30/00):
      Lot Number 7230309, Beginning date 6/16/2023 and Filling Ending date 6/17/2023
      Lot Number 7230310, Beginning date 6/19/2023 and Filling Ending date 6/21/2023
      Lot Number 7230311, Beginning date 6/20/2023 and Filling Ending date 6/21/2023
   i. FDA Registration Number, if any (11xxxxx): ANDA No. 210560

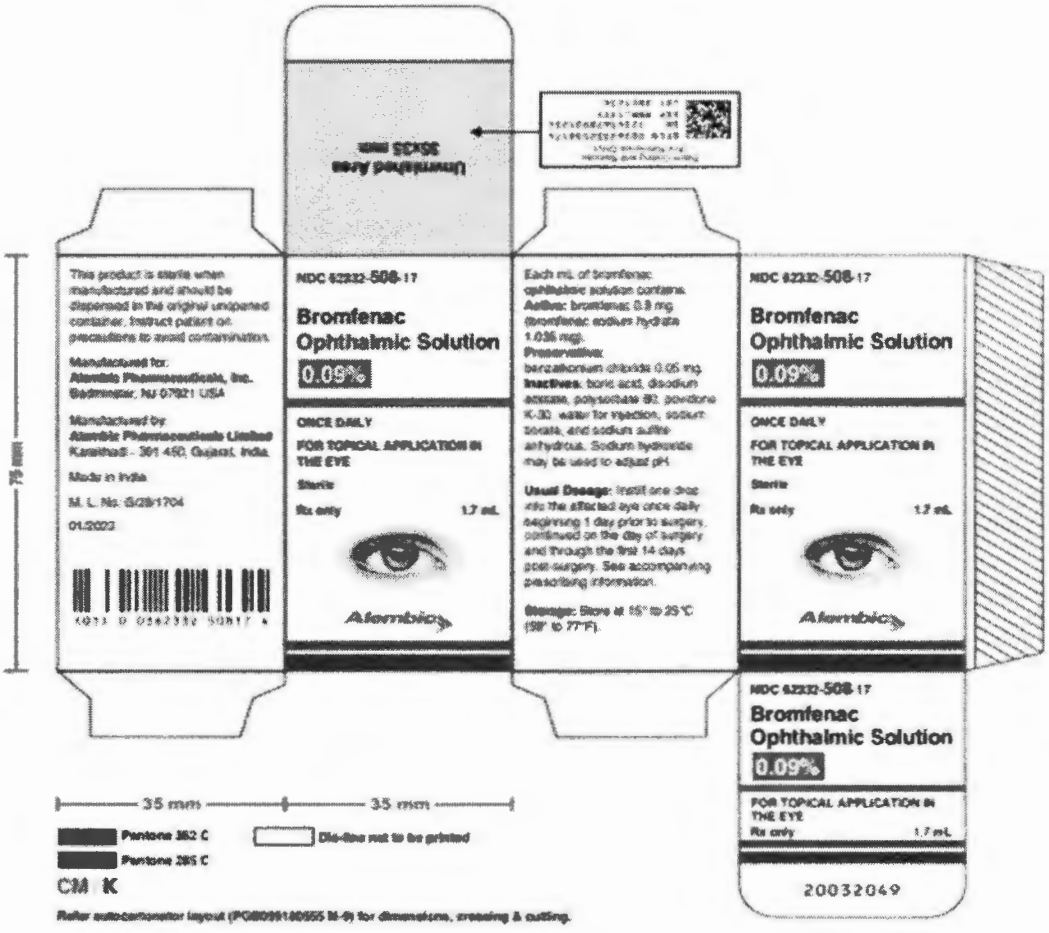
j. Container size and type for each product: 5mL white LDPE screw neck bottle with a LDPE white nozzle and HDPE gray cap

k. Two complete sets of label/labeling for each recalled product including:

o Product labeling (including ALL private labels) --Attached as annexure A



- Individual package label --Attached as annexure B



- Case label (photocopy acceptable)

o Package Inserts -- Attached as Annexure C

Open Size: 110x448 mm
Close Size: 110x28 mm
Drawing No.: PGB099180555 LF3 M-1

Black

Alembic

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 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

Instill one drop into the affected eye once daily beginning 1 day prior to surgery, continued on the day of surgery and through the first 14 days post- surgery **(2.1)**.

DOSAGE FORMS AND STRENGTHS

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

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)**

200320S0

ADVERSE REACTIONS

The most commonly reported adverse reactions in 2.7% of patients were abnormal sensation in eye, conjunctival hyperemia and eye irritation (including burning/stinging) **(6.1)**.

To report SUSPECTED ADVERSE REACTIONS, contact Alembic Pharmaceuticals Inc. at 1-866-210-9797 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 01/2023

FULL PRESCRIBING INFORMATION:
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*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

For the treatment of postoperative inflammation in patients who have undergone cataract extraction, one drop of bromfenac ophthalmic solution should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, continued on the day of surgery, and through the first 14 days 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.

448 mm

5.6 Contact Lens Wear
Bromfenac should not be administered while wearing contact lenses.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience
The most commonly reported adverse experiences 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 events were reported in 2-7% of patients.

6.2 Post-Marketing Experience
The following events 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 events 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)***)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects: Pregnancy Category C. Reproduction studies performed in rats at oral doses up to 0.9 mg/kg/day (1300 times the recommended human ophthalmic dose [RHOD]) and in rabbits at oral doses up to 7.5 mg/kg/day (11,000 times RHOD) revealed no evidence of teratogenicity due to bromfenac. However, 0.9 mg/kg/day in rats caused embryo-fetal lethality, increased neonatal mortality, and reduced postnatal growth. Pregnant rabbits treated with 7.5 mg/kg/day caused increased post implantation loss.

There are no adequate and well-controlled studies in pregnant women. 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.

Nonteratogenic Effects:
Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of bromfenac ophthalmic solution during late pregnancy should be avoided.

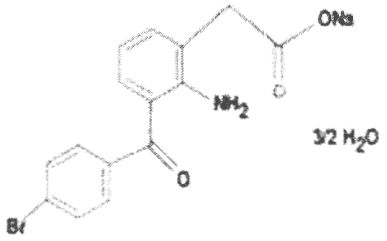
8.3 Nursing Mothers
Caution should be exercised when bromfenac is administered to a nursing woman.

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 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 (equivalent to 0.9 mg bromfenac free acid). Bromfenac sodium is designated chemically as sodium 2-amino-3-(4-bromobenzoyl) phenylacetate sesquihydrate, with an empirical formula of $C_{15}H_{11}BrNNaO_3 \cdot 3/2\,H_2O$. 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 hydrate 0.1035%
Preservative: benzalkonium chloride (0.05 mg/mL)
Inactives: boric acid, disodium edetate (0.2 mg/mL), polysorbate 80 (1.5 mg/mL), povidone K-30 (20 mg/mL), sodium borate, and sodium sulfite anhydrous (2 mg/mL). Sodium hydroxide may be used 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 (0.045 mg) 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 (900 times the recommended human ophthalmic dose [RHOD] of 1.67 mcg/kg in 60 kg person on a mg/kg basis, assuming 100% absorbed) and 5 mg/kg/day (7500 times RHOD), 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 (1300 and 450 times RHOD, respectively).

14 CLINICAL STUDIES

14.1 Ocular Inflammation and Pain Following Cataract Surgery

Clinical efficacy was evaluated in three randomized, double-masked, placebo controlled trials in which subjects requiring cataract surgery were assigned to Bromfenac ophthalmic solution or placebo. Patients were dosed with one drop per eye starting the day before surgery and continuing for 14 days. The primary endpoint was clearing of ocular inflammation by day 15. An additional efficacy endpoint was the number of patients who were pain free on day 1 after cataract surgery.

In 2 of the 3 studies, bromfenac ophthalmic solution had statistically significant higher incidence of completely clearing inflammation (46-47% vs. 25-29%) and also had a statistically significant higher incidence of subjects that were pain free at day 1 post cataract surgery (83-89% vs. 51-71%).

16 HOW SUPPLIED/STORAGE AND HANDLING
Bromfenac Ophthalmic Solution 0.09% is supplied in a white LDPE screw neck bottle with a LDPE white nozzle and HDPE gray cap as follows:
1.7 mL in 5 mL container - NDC 62332-508-17

STORAGE:
Store at 15° to 25°C (59° to 77°F)

17 PATIENT COUNSELING INFORMATION
17.1 Slowed or Delayed Healing
Patients should be advised of the possibility that slow or delayed healing may occur while using NSAIDs.

17.2 Sterility of Dropper Tip
Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

17.3 Concomitant Use of Contact Lenses
Contact lenses should not be worn during the use of this product.

17.4 Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines should be administered at least 5 minutes apart.

Rx Only

Manufactured for:
Alembic Pharmaceuticals, Inc.
Bedminster, NJ 07921, USA

Made in India.

Manufactured by:
Alembic Pharmaceuticals Limited
Karakhadi - 391 450, Gujarat, India.

Revised: 01/2023

20032050

448 mm

- Directions for Use:

  Not Applicable

- Promotional Material (if applicable):

  Not Applicable

l. Number of units packed per shipping carton/case: 160 bottles / shipper.

(Each bottle is packed in mono carton, 10 mono cartons packed in E-flute box, 16 such E-flute boxes packed in a shipper)

m. Expiration/Use By date:

Lot Number 7230309, Expiration date 5/31/2025

Lot Number 7230310, Expiration date 5/31/2025

Lot Number 7230311, Expiration date 5/31/2025

n. Expected shelf life of product (how long product is expected to be on the shelf; not necessarily expiration date): 24 Months

2. CODE(S):

List all batch numbers, lot numbers and/or serial numbers, product numbers, catalog numbers, packer or manufacturer numbers, pull date (exp. date), etc.

Lot Number 7230309, Expiration date 5/31/2025

Lot Number 7230310, Expiration date 5/31/2025

Lot Number 7230311, Expiration date 5/31/2025

3a. RECALLING FIRM:

Provide complete name and address of your firm. (Please include full name, full address, telephone and telefax number). Identify firm type (i.e., manufacturer, importer, broker, repacker, own label distributor, etc.)

Manufacturer:

Alembic Pharmaceutical Limited, Formulation Division III

Survey No. 779/790, Village: Karakhadi, Tal. Padra, District Vaodara, Pin-391450. Gujarat, India.

Telephone - +91-2662-670700, +91-2662-672608, +919879561480

Alembic Pharmaceuticals Limited is own label distributor.

3b. MANUFACTURER:

Provide complete name and address of manufacturer, if different from recalling firm. (Please include full name, full address, telephone and telefax number.)

Alembic Pharmaceutical Limited, Formulation Division III
Survey No. 779/790, Village: Karakhadi, Tal. Padra, District Vaodara, Pin-391450, Gujarat, India.
Telephone - +91-2662-670700, +91-2662-672608, +919879561480

4. REASON FOR RECALL:

a. State simply **WHY** your firm decided to recall the product(s).

- o If recall is due to the presence of a foreign object, describe foreign objects' size, composition, hardness, sharpness, etc.;
- o If recall is due to presence of contamination, explain level of contamination;
- o If recall is due to a label/ingredient issue, provide and identify the correct and incorrect label(s), description(s), ingredients, etc.

This recall has been initiated due to out of specification results observed in 18 Month long term stability analysis of Batch Nos. 7230310 and 7230311 at long term stability condition for the Related substance test for the Specified unidentified impurity at RRT about 1.06. The results are tabulated as below:

Table – 1: Out of specification results

Test / Specification	7230310	7230311
Specified unidentified impurity at RRT about 1.06: Specification: NMT 0.2%	0.27%	0.27%

As a part of investigation control sample testing was initiated for first three commercial batch No. 7230309, 7230310 and 7230311, where results of Batch No. 7230309 also found to be on higher side. Hence, recall is initiated for all the three batches. The results are tabulated as below:

Table – 2: Control sample test results:

Test / Specification	7230309	7230310	7230311
Specified unidentified impurity at RRT about 1.06: Specification: NMT 0.2%	0.24%	0.18%	0.21%

b. How and when did your firm **DISCOVER THE REASON** for recall [problem description]?

Out of specification results observed in 18 Month long term stability analysis of Batch Nos. 7230310 and 7230311 for the Related substance test for the Specified unidentified impurity at RRT about 1.06 on 04 April 2025.

c. What is the **ROOT CAUSE** of the reason for recall?

Include any analytical finding in qualitative and/or quantitative terms, indicating whether your firm's analysis or private laboratory was involved. Provide copies of test results/lab results, Analytical Work Sheets, which support the reason for recall. Details for any Field Alert submitted. Explain why the problem affects only those products/lots subject to the recall. Explain if the problem/defect affects ALL units subject to recall, or just a portion of the units being recalled.

The most probable reason for the generation of impurity at 1.06 is oxidation. The possibility of oxidative degradation may be attributed to the raw material used in the formulation of this product. Povidone K-30 is used as an excipient (viscosity enhancer) in the drug product. The Povidone K-30 specification is having peroxide content limit of ≤ 400 ppm. The lot of Povidone K-30 used in the OOS batches (Batch No: 72100480) was opened multiple times for sampling and dispensing. This could have resulted in higher peroxide content in the excipient at the time of usage in the OOS batches. The initial testing and periodic testing results of Povidone K-30 lot confirmed this observation.

Bromfenac ophthalmic solution 0.09% is filled in LDPE (Low Density Poly Ethylene) containers. Due to the semipermeable nature of the LDPE containers, the oxidative impurity can increase during the shelf life.

Corrective and preventive action:

The initial FAR has been submitted on 09th April 2025.

Following controls have been implemented as per SOP No. F3\WH\SOP\0063 titled "**Storage and Handling of Povidone (K-30)"** effective from 12-Sep-2024.

a) Each lot of Povidone K-30 received is dispensed into smaller multiple packs (each having quantity required for one batch) for manufacturing and analysis (required quantity for analysis) to avoid multiple opening and exposure of povidone K-30 to the environment.

b) Nitrogen Blanket / overlaying is done for the individual packs and these packs are fastened with cable tags / seal. The sealed pack containing Povidone K-30 shall be stored in triple laminated bag and sealed using sealing machine.

c) Before dispensing in batch, sample pack is tested for peroxide content and are released for usage only if the peroxide content is below 125 ppm. Based on this result the intact pack is issued for batch manufacturing.

d) BMR of product Bromfenac Ophthalmic Solution 0.09% (1.7 mL) was revised to register the Peroxide content in Povidone before initiating dispensing of API and excipients. If the peroxide content is less than 125 PPM, then only further batch dispensing is initiated. This will control the impurity level at RRT 1.06.

Impact on other batches

Following batches of Bromfenac Ophthalmic Solution 0.09% (1.7 mL) were manufactured with above controls:

Table – 3: Povidone K-30 results at the time of dispensing

Sr. No.	FG Batch No.	MFG Date	EXP Date	B. No. of Povidone used	Povidone test Results at the time of dispensing	Status
1	7230536	DEC-2023	NOV-2025	72301390	84 ppm (14-Dec-2023)	Commercial Batch
2	7240175	APR-2024	MAR-2026	72301390	111 ppm (11-Apr-2024)	Commercial batch. Part of Annual stability program
3	7240473	NOV-2024	OCT-2026	72400581	57 ppm (08-Nov-2024)	Commercial Batch
4	7250114	FEB-2025	JAN-2027	72400581	54 ppm (27-Feb-2025)	Commercial batch. Part of Annual stability program

There is adequate control implemented to control generation of impurity in subsequent batches, which helped to envisage that the batches would meet the Specification until end of shelf life. Further, control sample analysis of subsequent commercial batches were performed and are complying with the drug product specification.

Table – 4: Control sample test results

Specification Limit	**7230536**	**7240175**	**7240473**	**7250114**
Age of batch since manufacturing	16 Months	12 Months	4 months	2 months
Specified unidentified impurity at RRT about 1.06: NMT 0.2%	BQL	BQL	0.0483	BDL

BDL= Below Detection level (0.013%), BQL=Below Quantification Level (0.039).

From the above table, it can be understood that the batches, which have crossed 12 and 16 months, are having impurity level Below Quantification level (BQL).

The control samples of these batches will be monitored for related substance including impurity at RRT 1.06 at different time points (12 months, 18 months and 24 months).

Based on the implemented control strategy to control the peroxide content in Povidone K-30 and control sample analysis results, the impact is limited to initial commercial process validation batches i.e. Batch Nos. 7230309, 7230310 & 7230311.

d. Is the root cause of the problem related to:

(i) **STERILITY** deficiency : YES [ ] NO [X]

(ii) **PACKAGING** deficiency: YES [ ] NO [X]

e. What type of **ILLNESS or INJURY** may be caused by the problem?

Alembic Pharmaceuticals Ltd also have similar approved product ANDA. Bromfenac ophthalmic solution 0.07%; ANDA # 214340.

The ingredients in formulations of Bromfenac ophthalmic solution 0.07%; ANDA # 214340 and Bromfenac ophthalmic solution 0.09%; ANDA # 210560 are similar (except for surfactant,

Tyloxapol, in Bromfenac ophthalmic solution 0.07% and Polysorbate 80 in Bromfenac ophthalmic solution 0.09%).

Impurity profile of Bromfenac ophthalmic solution 0.07%; and Bromfenac ophthalmic solution 0.09% were evaluated and found to be similar.

Table – 5: Specification comparison

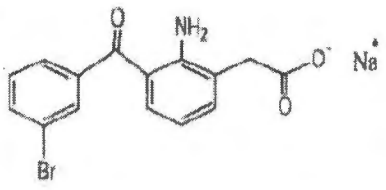
Bromfenac Ophthalmic solution 0.09%	**Shelf life specification Limit**	**Bromfenac Ophthalmic solution 0.07%**	**Shelf life specification Limit**
Impurity A 7-(4-Bromobenzoyl)-1, 3-dihydro-2H-indole-2-one.	NMT 1.0%	Impurity B [7-(4-Bromobenzoyl)-1,3-dihydro-2H-indole-2-One(Oxindole)]	NMT 1.0%
Specified unidentified impurity at RRT about 0.82	NMT 0.5%	Specified unidentified impurity at RRT about 0.85	NMT 0.1%
Specified unidentified impurity at RRT about 0.95	NMT 0.5%	Specified unidentified impurity at RRT about 0.96	NMT 0.6%
Specified unidentified impurity at RRT about 1.06	**NMT 0.2%**	**Specified unidentified impurity at RRT about 1.03**	**NMT 0.5%**
Specified unidentified impurity at RRT about 1.08	NMT 0.3%	Specified unidentified impurity at RRT about 1.09	NMT 0.3%
Any unspecified impurity	NMT 0.1%	Any unspecified impurity	NMT 0.1%
Total impurities (Including Adduct)	NMT 3.0%	Total impurities	NMT 2.4%

Method for related substances for both product were found to be similar for chromatographic parameter and diluent except there is a slight difference in mobile phase B composition and flow rate which lead to slight difference to elution pattern and RT/RRT of degradation products.

Fractions of Impurity eluted at RRT 1.06 in Bromfenac ophthalmic solution 0.09% and impurity at RRT 1.03 in Bromfenac ophthalmic solution 0.07% were collected and subject to mass spectroscopy.

Upon review of LCMS/ MS Q-TOF mass data, it was found that RRT based impurities shows Bromine isotopic pattern and are related to Bromfenac only due to its structural similarity to active (find below mass and structure of impurity)

Based on the spectroscopic information below is probable structure of the impurity

2-(2-amino-3-(3-bromobenzoyl) phenyl) acetate		$C_{15}H_{11}BrNO_3.Na$ 333.16/22.99	331.99

Review of toxicological assessment

Toxicological assessment of impurity having mass of 331.99 (molecular formula C15H11BrNO3.Na) using Derek nexus prediction was performed and it was found that particular impurity is non-mutagenic.

The results from Derek nexus showed inactive and equivocal prediction for mutagenicity. There are no structural alerts activated in Derek Nexus and no positive hypothesis associated with the query compound.

Based on report result, an overall in silico prediction of negative can be made for Bromfenac impurity. Therefore, it can be classified into class 5 as per classification of ICH M7 and hence, can be treated as non-mutagenic and non-carcinogenic impurity.

Impurity in Bromfenac ophthalmic solution 0.07% is having approved limit of 0.5% (Specified unidentified impurity at RT about 1.03) whereas structurally same impurity is having stringent limit of 0.2% in Bromfenac ophthalmic solution 0.09% (Specified unidentified impurity at RRT about 1.06)

Based on above discussion and data of Batch No. 7230309, 7230310 and 7230311 (expiry date: May-2025) it can be inferred that though impurity at RRT 1.06 is out of specification per Bromfenac ophthalmic solution 0.09% however said impurity is complying to approved specification for Bromfenac ophthalmic solution 0.07% and thus it will not have any patient safety risk.

Toxicity related risk evaluation:

Toxicity evaluation for impurity at RRT 1.06 has been performed. The impurity is structurally same as that of impurity at RRT 1.03 in approved ANDA #214340; Bromfenac ophthalmic solution 0.07% and approved with limit of NMT 0.5%. The QSAR based toxicity assessment confirm that impurity is non-mutagenic and non-carcinogenic impurity.

Health Hazard Evaluation:

Considering the limited toxicity profile as well as limited information regarding adverse drug reaction of identified impurity, the likelihood of serious adverse health effects from the affected batches is unlikely.

f. What is the **TOTAL** number of reports of **ILLNESS or INJURY COMPLAINTS** received regarding recall product? (Date of complaint, description of complaint – include details of any injury or illness, lot number involved). Please provide copies of such report.

No market complaint or No reports of illness or injury complaints are received.

g. What is the **TOTAL** number of reports of **PRODUCT DEFECT COMPLAINTS** received regarding the recall product? (Please provide copies of such report.)

There are no Product defect complaints for the said product till date.

h. Have you done any **HEALTH HAZARD EVALUATIONS** and/or Health Risk Assessments associated with the recall product?

(No health consequences, minor/major health consequences, potential serious risk of patient injury, potential risk of a serious or life threatening allergic reaction/DEATH!)

No health consequences have been identified.

i. List corrective measures taken to **PREVENT SIMILAR OCCURRENCE** of the problem. (Include copies of documents pertaining to verification of training or SOP changes, documents pertaining to product QA, design control, specifications, validation of software, etc., as appropriate.)

Following controls have been implemented as per SOP No. F3\WH\SOP\0063 titled "**Storage and Handling of Povidone (K-30)"** effective from 12-Sep-2024.

a) Each lot of Povidone K-30 received is dispensed into smaller multiple packs (each having quantity required for one batch) for manufacturing and analysis (required quantity for analysis) to avoid multiple opening and exposure of povidone K-30 to the environment.

b) Nitrogen Blanket / overlaying is done for the individual packs and these packs are fastened with cable tags / seal. The sealed pack containing Povidone K-30 shall be stored in triple laminated bag and sealed using sealing machine.

c) Before dispensing in batch, sample pack is tested for peroxide content and are released for usage only if the peroxide content is below 125 ppm. Based on this result the intact pack is issued for batch manufacturing.

d) BMR of product Bromfenac Ophthalmic Solution 0.09% (1.7 mL) was revised to register the Peroxide content in Povidone before initiating dispensing of API and excipients. If the peroxide content is less than 125 PPM, then only further batch dispensing is initiated. This will control the impurity level at RRT 1.06.

5. VOLUME OF PRODUCT IN COMMERCE:

a. What is the TOTAL amount of recall product that was **manufactured (include dates of manufacture)**? 57,290 Bottles

Lot 7230309 Manufactured 6/2023- 18,600 bottles

Lot 7230310 Manufactured 6/2023- 19,360 bottles

Lot 7230311 Manufactured 6/2023- 19,330 bottles

b. What is the TOTAL amount of recall product distributed in **commerce**? 46,831Bottles

Lot 7230309 14,860 bottles

Lot 7230310 14,400 bottles

Lot 7230311 17,560 bottles

c. What is the TOTAL amount of recall product **remaining** at your firm?

0 bottles

d. What were the **DATES** of distribution? **Give both beginning and ending dates.**

(e.g. 1/14/00 to 4/15/00)

10/19/2023- 5/29/2024

Lot 7230309 10/19/2023-5/29/2024

Lot 7230310 11/3/2023-3/20/2024

Lot 7230311 1/12/2023-5/29/2024

e. Provide an **ESTIMATE** (%) of the amount of product that may be recovered.

46 bottle or .1% of total distributed

6. DISTRIBUTION PATTERN:

a. What is the TOTAL number of **consignees** (customers) that received the recall product?

19 customers

b. What is the TOTAL number of **wholesaler dealers** that received the recall product?

4 wholesalers

c. What is the TOTAL number of **distributors** that received the recall product?

6 distributors

d. What is the TOTAL number of **retailers** that received the recall product?

9 retailers

e. What is the TOTAL number of **consumers/users** that received the recall product?

0 consumers/users

f. Where is the recall product **distributed**?

(Indicate worldwide/nationwide/statewide and **name the U.S. States,** e.g., CA, NV,)

(Provide a list of the consignees (by state or province) with their FULL ADDRESSES with PHONE NUMBERS.)

g. Were there any product distributed to U. S. Defense Supply Center, VA or other Federal Government Agency sales/distribution centers or foreign countries? No

(Provide separate lists via and excel spread sheet of **foreign, domestic, government and Canadian consignees** with full addresses by state order.)

Number of Domestic Consignees: ___19___

Number of Foreign Consignees: ___0___

Consignees	Approx. Number	Consignees	Approx. Number
Distributor	6	Repacker/Relabeler	0
Retailer	9	Direct Accounts	0
Institution	0	Veterans Administration	0
Medical Facility	0	Department of Defense	0
Internet Sales	0	Manufacturer	0
Physician	0	USDA	0
Consumer/Patient	0	Other (Wholesalers)	4

7. FIRM'S RECALL STRATEGY:

Following questions are provided to assist you in describing your recall strategy in **DETAIL** as follows: Alembic Pharmaceuticals Inc, the US entity of Alembic Pharmaceuticals LTD, will be implementing the recall. Alembic Pharmaceuticals Inc (US) will directly call and contact the customers to notify them of the recall and assure the recall information is channeled to the correct person or customer recall center for implementation. The recall letter, response form, and

Inmar return form will be provided to each of the consignees. Alembic Pharmaceuticals Inc will initiate follow up calls to push customers to respond periodically (5-7 day intervals) after the initial notification. Additionally, Inmar will be utilized for mail notifications and follow up to retrieve any product still in the distribution channels.

(a) Include the **DATE** recall was initiated, if it is already underway or the DATE your firm plans to start the recalling process.

Recall process was started 5/6/25 with Alembic Pharmaceuticals Inc US initiating customer contact.

(b) How do you plan to **NOTIFY** all the consignees affected by this recall?

(press release, letter, telefax, telephone, e-mail, visit, etc.)

We will do a blend of calls and emails directly from Alembic Pharmaceuticals Inc US and indirectly though Inmar answering inquiries, providing return forms and kits, and mail follow up.

(c) How do you plan to undertake a **SUB-RECALL**? (If the product is distributed to wholesale dealers/distributors/retailers)

(provide follow-up letters to wholesalers, e.g., wholesalers are requested to forward copies of your recall letters and response forms to their customers, etc.)

The Inmar recall announcement letter is sent to each consignee with instructions to provide the letter to each customer where product was sold. We will follow up with each direct purchasing consignee to verify that the process letter was sent to the purchasing customer.

(d) How do you plan to monitor the number of consignees **NON-RESPONDING** to the recall communication?

(include envelopes and return/reply cards, via response form mailed, certified mailing with return receipt, visit, telephone follow-up call, etc.)

Alembic Pharmaceuticals US will follow up through phone calls and emails. Inmar will send trackable mailings to verify information was received by each consignee.

(e) How do you plan to do **EFFECTIVENESS CHECKS** of this recall?

(by response form mailed?, certified mailing with return receipt, etc.)

(telefax, telephone, e-mail, visit, follow-up letter, etc.)

Alembic Pharmaceuticals US will follow up through phone calls and emails. Inmar will send trackable mailings to verify information was received by each consignee.

(f) Date your firm ceased further distribution of the product(s).

The product was viewed to be short dated as of 5/29/2024. We discontinued sales as of 5/.29/2024. The product being recalled expires 5/31/2025 and we anticipate very little product remaining with any customer.

(g) How do you plan to **STORE** the recall product? (if returned)

(quarantine, locked stored, etc.)

[NOTE: It is equally important to assure that all returned merchandise is promptly inventoried, handled, and stored in such a manner as to assure its separation from acceptable materials so it will not inadvertently be used or shipped. Our past experience in similar situations has shown that the longer a defective product is held between the initiation and termination of a recall, the greater the chance of its accidental misuse.]

Inmar will be utilized to receive, inventory, store, and eventually destroy the returned product

(h) How do you plan to **DISPOSE** the recall products?

(destroy, recondition, correct label, field correct by firm's personnel, etc.)

Product will be destroyed by Inmar

Please Note: Any destruction or reconditioning of recalled items may require FDA supervision.

8. FIRM OFFICIAL:

Full name, including middle initial, of the most responsible individual (with title) to contact regarding the recall. Please include full address, telephone, fax number and e-mail address.

David M. Cobb
550 Hills Drive, Suite 104B
Bedminster, NJ 07921
Phone: 908-552-5839
Fax: 908-393-9605
Emai: david.cobb@alembicusa.com

9. PRESIDENT/Most Responsible of the firm:

Please include full name, including middle initial, full address, telephone, fax number and e-mail address.

PLEASE PROVIDE THE FOLLOWING DOCUMENTS:

PRODUCT LABEL(s): (Label(s) and labeling(s)

CUSTOMER LETTER(s): (Notification letter(s) to consignees, recall letter(s) or voluntary recall letter(s)

DISTRIBUTION LIST: (List of consignees or list of customers, INCLUDE FULL STREET ADDRESSES with PHONE NUMBERS), sorted by state **as an** Excel spreadsheet with tabs separating DoD, VA, and Foreign customers.

PRODUCT CATALOG: (if applicable)

TEST RESULT(s): (Analytical Work Sheet, Failure Analysis Worksheet, Lab. results, etc. and methodology used)

DOCUMENT(s): (Health Risk Assessment, Product QA, Specification Sheet, SOP changes, complaint follow-up investigation, etc.)

PRESS RELEASE: (News release, allergy alert, if applicable)

Thank you for your cooperation and efforts.

STOCK RESPONSE FORM

Pharmacy Recall of Bromfenac Ophthalmic Solution 0.09%
Lots 7230309, 7230310, 7230311
Retail Level
(05/07/2025)

Please fill out this form completely. By doing so, this will acknowledge that you have read and understand the recall instructions and have taken the appropriate action.

Customer Name _____ DEA #_____

**DEA # is required, if it is not provided, the processing of your form will be delayed.*

Address_____

City_____ State_____ Zip_____

Contact Name (please print)_____ Telephone #_____

Contact Signature _____ Date_____

I have checked my stock and:

_____Do not have any stock of the **recall product**.

OR

I have quarantined and listed in the box below the quantity of recall units and I will be returning to Inmar, as soon as possible. Upon receipt of this Response Form, Inmar, will issue return authorization label(s) Please indicate the # of needed box labels _____.

Item Description	NDC	Lot #	Qty returning
Bromfenac Ophthalmic Solution 0.09%	**62332-508-17**	7230309	
Bromfenac Ophthalmic Solution 0.09%	**62332-508-17**	7230310	
Bromfenac Ophthalmic Solution 0.09%	**62332-508-17**	7230311	

If you did not purchase the product directly from the Manufacturer, please complete the below section.

Purchased From: Wholesaler Name _____ DEA #_____

City_____ State_____

If you have any questions regarding this form or product return please contact Inmar at 1-800-967-5952. Office hours 9am to 5pm EST Mon thru Fri.

Please fax this form to: 1-817-868-5362 or E-mail rxrecalls@inmar.com

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SITE ADDRESS : ***ALEMBIC PHARMACEUTICALS LIMITED*** (FORMULATION DIVISION-III, KARAKHADI)
FACTORY : SURVEY NO. 779/790, KARAKHADI, TAL. PADRA, DIST. VADODARA, PIN-391450, GUJARAT.
CIN No. : L24230GJ2010PLC061123, **PAN No. :** AAICA5591M