PRODUCT MONOGRAPH

[Pr]Eugia-Bromfenac

Bromfenac Ophthalmic Solution

Solution, 0.07% w/v bromfenac (as bromfenac sodium sesquihydrate), Ophthalmic

Non-steroidal Anti-inflammatory Agent

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0.07 % w/v (as bromfenac sodium sesquihydrate)
Topical Ophthalmic Solution 0.07 % w/v

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Non-medicinal Ingredients
Topical Ophthalmic	Ophthalmic Solution Bromfenac 0.07% w/v (as bromfenac sodium sesquihydrate)	Boric Acid, Benzalkonium Chloride, Edetate Disodium, Povidone, Sodium Borate, Sodium Sulfite, Tyloxapol, Sodium Hydroxide and water for injection.

INDICATIONS AND CLINICAL USE

Eugia-Bromfenac (bromfenac ophthalmic solution 0.07% w/v) is indicated for:
- treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery

Geriatrics (> 70 years of age)
No overall differences in safety and effectiveness have been observed between elderly and younger adult patients.

Pediatrics (< 18 years of age)
The safety and effectiveness in pediatric patients have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

Since there exists the potential for cross-sensitivity, Eugia-Bromfenac should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. (see Warnings and Precautions – General)

WARNINGS AND PRECAUTIONS

General

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory drugs (NSAIDs), including Eugia-Bromfenac. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Eugia-Bromfenac contains sodium sulfite, which 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.

Ophthalmologic

Corneal Effects and keratitis
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, including Eugia-Bromfenac, 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.

Delayed Healing
All topical NSAIDs may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Rebound inflammatory effect (macular edema)
Post-marketing experience indicates that in rare cases, upon withdrawal of bromfenac ophthalmic solution 0.07% w/v, a flare-up of the inflammatory response, in the form of macular edema, due to the cataract operation may occur. Patients may have to be monitored for occurrence of macular edema upon discontinuation of Eugia-Bromfenac.

Contact Lens Wear
Eugia-Bromfenac should not be instilled while wearing contact lenses. Remove contact lenses

prior to instillation of Eugia-Bromfenac. The preservative in Eugia-Bromfenac, benzalkonium chloride may be absorbed by soft contact lenses. Lenses may be reinserted 15 minutes after administration of Eugia-Bromfenac.

Hematologic

Bleeding
With some NSAIDs, including Eugia-Bromfenac, 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 Eugia-Bromfenac ophthalmic solution be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Carcinogenesis and Mutagenesis

Carcinogenicity and mutagenicity have not been studied in humans; see TOXICOLOGY.

Special Populations

Pregnant Women:
There are no studies with bromfenac ophthalmic solution in pregnant women. Eugia-Bromfenac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of Eugia-Bromfenac during late pregnancy should be avoided.

Studies in rats and rabbits produced no clear treatment-related malformations in reproduction studies at doses up to 90 times (for rats) and 150 times (for rabbits) the recommended human ophthalmic dose [RHOD], there was however, embryo-fetal lethality and maternal toxicity.

See TOXICOLOGY - Reproduction and Development.

Nursing Women
Eugia-Bromfenac should not be administered to a nursing woman unless the potential benefit justifies the potential risk to the fetus. No specific studies have been performed to evaluate bromfenac sodium levels in the milk of lactating women associated with topical administration. However, bromfenac is excreted in milk of lactating female rats. See Animal Pharmacokinetics - Metabolism and Excretion.

Pediatrics (< 18 years of age)
The safety and effectiveness of bromfenac ophthalmic solution in pediatric patients have not been established.

Geriatrics (> 70 years of age): No overall differences in safety and effectiveness have been observed with bromfenac ophthalmic solution between elderly and younger patients.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Two multi-centre, randomized, double-masked, parallel-group and placebo (vehicle)-controlled, phase 3 studies of identical design (S00124 ER and S00124 WR) evaluated the efficacy and safety of bromfenac ophthalmic solution as compared with vehicle in the treatment of ocular inflammation and pain associated with cataract surgery.

The safety analyses were conducted on the Safety population, which included all randomized subjects undergoing cataract surgery who received at least 1 dose of investigational product (IP). In the pooled studies, a total of 416 patients were randomized with 212 receiving bromfenac ophthalmic solution alone and 204 receiving vehicle once daily beginning one day prior to surgery, continuing on the day of surgery, and through the first 14 days post-surgery.

Overall, the proportion of patients who experienced any adverse event (AE) was significantly greater in patients with placebo (42.6%), as compared to those with bromfenac ophthalmic solution (28.8%).

Similarly, the proportion of patients who experienced an AE related to the investigational product (adverse drug reaction) affecting the study eye or both eyes was higher in the pooled placebo group (21.1%) than in the pooled bromfenac 0.07% group (6.6%). See Table 1. Some of the adverse events may have been the result of the cataract surgical procedure itself, rather than the investigational products.

IOP measurements were performed at pre-specified time points during the study. At Day 1 (post- operative) increases from baseline IOP $\geq$ 10 mm Hg were recorded more frequently in patients treated with bromfenac ophthalmic solution (5.7%, n=12), as compared to those receiving Placebo (2.5%, n=5) but not thereafter.

Table 1: Summary of AEs Affecting the Study Eye and Related to IP with an Incidence ≥2.0% (Safety Population, S00124 Pooled Studies)

Preferred Term (MedDRA 14.0)	**Bromfenac 0.07% QD Studies**	
	Bromfenac 0.07% QD N = 212	**Placebo QD N = 204**
Subjects reporting an IP-related adverse event affecting the Study Eye or Both Eyes	14 (6.6%)	43 (**21**.1%)
Anterior chamber inflammation	5 (2.4%)	11 **(5.**4%)
Conjunctival hyperemia	2 (0.9%)	8 (**3.9%)**
Corneal edema	1 (0.5%)	5 (2.5%)
Lacrimation increased	1 (0.5%)	5 (2.5%)
Eye pain	6 (2.8%)	16 (**7.8**%)
Ocular hyperaemia	0	4 (2.0%)
Foreign body sensation in eyes	0	5 (2.5%)
Photophobia	1 (0.5%)	8 (3.9%)

Note: Subjects who reported the same AE more than once were counted once for each higher level or preferred term.
Note: An event was considered related to IP if the relationship was 'possible', 'probable', or 'definite'.
Incidence was defined as the number of subjects reporting an AE per the number of subjects in the safety population.

The most commonly (with an incidence ≥2.0%) reported adverse reactions following use of bromfenac ophthalmic solution after cataract surgery included eye pain and anterior chamber inflammation. AEs with an incidence ≥2.0% were experienced more frequently in the placebo group than the bromfenac treatment group. The most commonly reported AEs with ophthalmic NSAIDs have been generally associated with the cataract surgery rather than the medication alone.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Eye Disorders: conjunctival hyperemia, conjunctival oedema, corneal oedema, corneal abrasion, uveitis, increased lacrimation, eyelid oedema, photophobia, blurred vision.

Abnormal Hematologic and Clinical Chemistry Findings

No laboratory abnormalities were reported as adverse events in any of the clinical studies.

Post-Market Adverse Drug Reactions

Post-marketing experience indicates that in rare cases, upon withdrawal of bromfenac ophthalmic solution, a flare- up of the inflammatory response, in the form of macular oedema, due to the cataract operation may occur.

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. These may include keratitis, epithelial breakdown, corneal thinning, corneal erosion,

corneal ulceration or corneal perforation. 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.

DRUG INTERACTIONS

Drug-Drug Interactions

No specific drug interaction studies have been conducted with bromfenac ophthalmic solution in humans. For animal data, see **DETAILED PHARMACOLOGY - Metabolism and Excretion.**

All topical 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.

It is recommended that Eugia-Bromfenac be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time. (see Haematologic Section).

Drug-Food Interactions

Interactions with food have not been studied in humans. Since Eugia-Bromfenac is administered topically, the presence of food is not expected to have a significant effect on ocular bioavailability.

Drug-Laboratory, and Drug-Herb Interactions

Interactions with laboratory tests, and interactions with herbal products have not been studied.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Eugia-Bromfenac (bromfenac ophthalmic solution 0.07% w/v) is administered by instillation into the affected eye. It is indicated for topical ophthalmic use only.

Bromfenac ophthalmic solution has not been studied in pediatric patients, pregnant or nursing women and patients with hepatic impairment. Therefore, no specific dosage recommendations can be made for these patients.

Recommended Dose and Dosage Adjustment

One drop of Eugia-Bromfenac should be applied to the affected eye once daily beginning 1 day prior to cataract surgery, and continued on the day of surgery, and through the first 14 days of the postoperative period.

Missed Dose

If a dose is missed, it should be applied as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped, and the regular dosing schedule should be resumed.

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 of the postoperative period. Discard any unused eye drops 28 days after opening.

Use with Other Topical Ophthalmic Medications

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

Contact Lens Wear

Eugia-Bromfenac should not be instilled while wearing contact lenses.

If contact lenses use is recommended by the physician, they should be removed prior to instillation of Eugia-Bromfenac and may be re-inserted 15 minutes following administration of Eugia-Bromfenac.

The preservative in Eugia-Bromfenac, benzalkonium chloride, may be absorbed by soft contact lenses.

OVERDOSAGE

There are no data on accidental or deliberate overdose with bromfenac ophthalmic solution. If Eugia-Bromfenac is accidentally ingested, drink fluids to dilute.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Bromfenac is a non-steroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of action is thought to be due to the drug's ability to block prostaglandin synthesis by inhibiting cyclooxygenase (COX) 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.

Pharmacodynamics

In earlier studies the basic mechanism of action along with anti-inflammatory, anti-pyretic, and analgesic effects were examined using various in vitro and in vivo techniques. See DETAILED PHARMACOLOGY – Pharmacodynamics.

Pharmacokinetics

Absorption

Following ocular topical dosing, four times daily for 28 days in healthy human subjects, it was suggested that the bromfenac plasma concentration was very low (possibly $\leq$ 50ng/ml). Systemic exposure following treatment with bromfenac ophthalmic solution is expected to be very low and of little clinical significance when bromfenac ophthalmic solution is used as directed. After oral administration, bromfenac has been shown to be absorbed into the systemic circulation.

Distribution

No human studies are available; however, studies in rabbits have shown that ^{14}C-bromfenac is extensively distributed throughout the eye following a single topical administration. See animal studies in DETAILED PHARMACOLOGY - Pharmacodynamics.

Bromfenac shows high affinity for binding to mammalian plasma proteins. *In vitro*, 99.8% of bromfenac was bound to proteins in human plasma. In rabbits, Bromfenac is distributed to pigment rich ocular tissues, however, no biologically relevant binding to melanin was observed *in vitro*. See DETAILED PHARMACOLOGY - Protein Binding.

Metabolism

Although no studies have been conducted regarding the sites of metabolism for ophthalmic bromfenac, a study in human volunteers orally treated with radiolabelled ^{14}C-bromfenac, suggested that, unchanged parent compound was the predominant component in plasma, and metabolites of bromfenac were predominant in urine.

Excretion

Following oral administration of ^{14}C-bromfenac to healthy human volunteers, the majority of

radioactivity was detected in the urine, which accounted for approximately 82% of the dose, while fecal elimination represented approximately 13% of the dose.

Special Populations and Conditions

The pharmacokinetics of bromfenac sodium have not been studied specifically in special populations (e.g., pediatrics, geriatrics, gender, race, genetic polymorphism) or certain conditions (e.g., hepatic insufficiency).

STORAGE AND STABILITY

Store at 15° - 25°C.
Discard 28 days after opening.

SPECIAL HANDLING INSTRUCTIONS

To minimise the chance of contamination of the dropper tip and bromfenac solution, patients are advised to replace the bottle cap after use, and to avoid touching the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Patients are advised that a single bottle of Eugia-Bromfenac is used to treat only one eye.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Eugia-Bromfenac contains 0.805 mg bromfenac sodium sesquihydrate (equivalent to 0.7 mg bromfenac free acid) per mL, supplied as a 0.07% w/v topical ophthalmic solution.

Eugia-Bromfenac 0.07% w/v topical ophthalmic solution is supplied in white, round LDPE bottle with grey cap and tamper evident seal as shrink band around closure and neck area of the bottle of 3 mL for commercial sizes, preserved with Benzalkonium Chloride 0.005%, and the following inactive ingredients: Boric Acid, Edetate Disodium, Povidone, Sodium Borate, Sodium Sulfite, Tyloxapol, Sodium Hydroxide to adjust pH and water for injection (or Purified Water).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Bromfenac Sodium Sesquihydrate

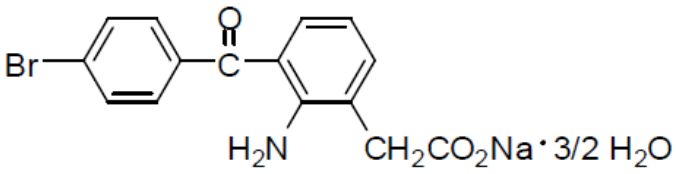
Code name: AHR-l0282B

Chemical name: Sodium 2-amino-3-(4-bromobenzoyl)phenylacetate sesquihydrate

Molecular formula: $C_{15}H_{11}BrNNaO_3 \cdot 3/2H_2O$

Molecular mass: 383.17 g/mol

Structural formula:



Physicochemical properties

Description: Bromfenac sodium sesquihydrate is a Yellow or orange yellow crystalline powder

Solubility: Freely soluble in water, soluble in methanol, practically insoluble in acetonitrile, acetone and chloroform

pH: 8.4-9.3 (50 mg/mL in water)

pKa: 4.29

CLINICAL TRIALS

Study demographics and trial design

Bromfenac ophthalmic solution for the treatment of postoperative inflammation and reduction of ocular pain was evaluated in two multi-center, randomized, double-masked, parallel-group and placebo (vehicle)-controlled trials.

Patients undergoing cataract surgery self-administered bromfenac ophthalmic solution or vehicle once daily (QD), beginning 1 day prior to surgery, continuing on the morning of surgery and for 14 days after surgery. Complete clearance of anterior chamber (AC) inflammation (0 AC cell and no AC flare) was assessed on Days 1, 3, 8 and 15 post-surgery using slit lamp biomicroscopy. The pain score was self-reported.

The patient population included adults who required unilateral cataract surgery (phacoemulsification or extracapsular) with posterior chamber intraocular lens (PCIOL) implantation and for whom no other ophthalmic surgical procedures (e.g., relaxing incisions, iridectomy, conjunctival excisions, etc.) were planned. Table 2 outlines the patient demographics for each of the trials.

Table 2: Summary of patient demographics for clinical trials in cataract surgery

Study #	Dosage, route of administration and duration	# Subjects by Arm Entered/ Completed	Mean age (Range)	Gender
Study 1	Bromfenac ophthalmic solution ophthalmic QD vs. placebo QD 16 days	Bromfenac ophthalmic solution: 112/109 placebo: 108/102	67.4 (39-87)	81M/139F
Study 2	Bromfenac ophthalmic solution ophthalmic QD vs. placebo QD 16 days	Bromfenac ophthalmic solution: 110/104 placebo: 110/100	69.5 (18-93)	72M/148F

Study results

The efficacy analyses were conducted on the intent to treat (ITT) population, which included all randomized subjects. In the ITT populations, a total of 440 subjects were assessed. Of these, a total of 220 subjects were randomized in Study 1 (112 treated with bromfenac ophthalmic solution; 108 treated with Placebo), and in Study 2 (110 treated bromfenac ophthalmic solution; 110 treated with Placebo).

The primary efficacy analysis for Study 1 and Study 2 was defined as the proportion of subjects achieving a complete clearance of ocular inflammation (zero cell and no flare) by Day 15 of the study (primary efficacy endpoint). The secondary efficacy endpoint (ocular pain) was determined by the proportion of subjects who were pain free at Day 1 (main secondary endpoint).

The proportion of subjects who had cleared ocular inflammation at Day 15 was significantly higher in the bromfenac ophthalmic solution group than in the placebo group for each study.

The proportions of subjects who were pain free were significantly higher in the bromfenac ophthalmic solution group than in the placebo group at Day 1 for each study. See results in Table 3.

Table 3: Summary of Results of Efficacy Studies (Intent-to-Treat Population)

Proportion of Subjects with Cleared Ocular Inflammation (0 AC cells and no AC flare) (primary efficacy endpoint at Day 15)				
Study	Visit	Bromfenac 0.07%	Placebo	Difference in rates (p-value)
Study 1	At Day 8	27/112 (24.1%)	7/108 (6.5%)	17.6% (p=0.001)
	At Day 15	51/112 (**45.5**%)	14/108 (**13.0**%)	**32.5%** (p <0.0001)
Study 2	At Day 8	33 /110 (30.0%)	15/110 (13.6%)	16.4% (p=0.0259)
	At Day 15	50/110 (**45.5**%)	31/110 (**28.2**%)	**17.3%** (p =0.0466)
Proportion of Subjects Who Were Pain Free				
Study	Visit	Bromfenac 0.07%	Placebo	p-value
Study 1	At Day 1	91/112 (81.3%)	47/108 (43.5%)	<0.0001*
Study 2	At Day 1	84/110 (76.4%)	61/110 (55.5%)	0.0017*

*p-value for Bromfenac versus Placebo was from a Fisher's exact test.

Similarly, the statistically significant difference between bromfenac 0.07% and placebo groups for the proportion of subjects that were pain free was also maintained at Day 8 and Day 15 in both studies.

DETAILED PHARMACOLOGY

Animal Pharmacodynamics

Bromfenac sodium inhibited both arachidonic acid and carrageenan-induced conjunctival edema in a dose-dependent manner, and the increase of aqueous humor protein typically seen in response to paracentesis and laser energy application. Bromfenac sodium demonstrated greater inhibition of acute chemosis in comparison with pranoprofen ophthalmic solution (PPF). Further, the inhibition of increased aqueous humor protein induced by paracentesis was 8 to 10 times greater than that seen with PPF. Bromfenac sodium ophthalmic solution instilled QID demonstrated significant inhibition in the experimental uveitis rabbit model (a chronic ocular inflammation model), and its effect was maintained when the frequency of instillation was reduced to BID. In the same model, PPF demonstrated significant inhibition when instilled QID but not BID.

Mechanism of Action

In a battery of experiments, bromfenac sodium was found to inhibit both cyclooxygenases 1 and

2, thereby inhibiting the inflammatory reactions induced by mediators such as prostaglandins. In studies to examine the mechanism of action, anti-inflammatory, anti-pyretic, and analgesic effects were observed. Bromfenac sodium was found to inhibit Evan's blue/carrageenan-induced pleural exudates and carrageenan-induced footpad edema more potently (equivalent action at a lower dose) than the comparator indomethacin. Bromfenac sodium at 0.8 mg/kg demonstrated antipyretic action equivalent to that observed with 4.0 mg/kg of indomethacin in a high body temperature rat model; the drug did not decrease normal body temperature in rats. Bromfenac sodium was found to be at least three times more potent than zomepirac and suprofen in blocking acetylcholine-induced abdominal constriction in mice, and approximately six times more potent than zomepirac at inhibiting the pain reaction to bradykinin at very low doses in dogs.

Animal Pharmacokinetics

Absorption and Distribution

Studies in animals have shown that following topical ocular administration, bromfenac is rapidly absorbed and distributed throughout the eye and systemic exposure is low.

In a study in which rabbits received a single topical instillation of ^{14}C- bromfenac, measurable concentrations were detected in the cornea, conjunctiva, sclera, iris/ciliary body, aqueous humor, lens, vitreous humor and retina/choroid. The highest concentration of radioactivity was observed in the cornea and conjunctiva, the primary target tissues. By 24 hours after dosing, <1% of the maximum radioactivity observed in the cornea and conjunctiva at 15 minutes post-dose was present. By 72 hours after instillation, concentrations were below the detection limit in all ocular tissues examined except for the lens. Following repeated topical administration of ^{14}C-bromfenac for 21 days, concentrations of radioactivity observed in the cornea and conjunctiva 24 hours following the last dose were similar to the levels observed at 24 hours following a single administration, suggesting that no accumulation occurs with repeated dosing.
Following a single 0.1 mg topical dose to rabbits, maximum concentrations of 113 ng•eq/mL were observed in the plasma after 30 minutes. The calculated plasma half-life was 2.2 hours, and the $AUC_{(0\text{-}12h)}$ was 156 ng•eq*hr/mL. Concentrations of bromfenac declined rapidly thereafter and were below the limit of quantitation (< 0.4 ng•eq/mL) by 24 hours. When ^{14}C- bromfenac was instilled into the eyes of rabbits once daily for 21 days, the plasma radioactivity concentration achieved steady state. Concentrations of bromfenac were 1.3 ± 0.2 ng•eq/mL 24 hours after the final dose and fell below the limit of quantitation by 168 hours post-dose.
Bromfenac is shown to be well absorbed after oral dosing and is distributed to most tissues after oral and intravenous administration. Following a single oral dose (1 mg/kg) to fasted rats, maximum concentrations in plasma (5.03 ng/mL) were observed 1 hour after dosing, with a half-life of approximately 4 hours. When compared with the exposure obtained following intravenous administration, the absolute oral bioavailability was approximately 44%.

Following a single oral administration of ^{14}C-bromfenac (2 mg/kg) to rats, the concentration of radioactivity was highest in the gastrointestinal tract, urinary bladder, liver, and kidneys. The radioactivity concentrations detected in other tissues were equivalent to or below the concentration in plasma. There was no apparent accumulation of radioactivity in any organ. Concentrations of radioactivity in the organs/tissues of monkeys were almost equivalent to those

noted in rats.

Concentrations of radioactivity were 2-fold to 8-fold lower in fetal placenta and plasma, respectively, compared to dams following a single oral dose of 0.9 mg/kg ^{14}C-bromfenac to female rats during pregnancy.

Metabolism and Excretion

Bromfenac is not extensively metabolized, with the parent compound representing the majority of the drug-related material in plasma whether the compound is administered orally or by topical instillation.

Following oral administration of ^{14}C-bromfenac to rats, the parent compound accounted for most of the drug-related material in plasma. A study using male and female rhesus monkeys also showed that bromfenac sodium accounted for most drug-related material in plasma, however there were differences in the metabolism profile of bromfenac sodium between species. When plasma and the anterior aqueous humor were investigated after instillation of ^{14}C-bromfenac to rabbits, the parent compound accounted for 70-80% of drug-related material in both matrices.

Liver cytochrome P450 activity was not affected following repeated oral administration of bromfenac (0.2, 1, 5, and 7.5 mg/kg) to mice for 7 days. Phenobarbital pre-treatment followed by intraperitoneal administration of bromfenac resulted in a slight but significant decrease in the concentrations of reduced glutathione in the liver and kidneys. However, the change was considered minor and not physiologically significant.

Bromfenac is excreted in the urine, feces, bile, and milk following oral and intravenous administration.

Following a single oral administration of ^{14}C-bromfenac (0.6 mg/kg) to male rats, 26.6% and 55.1% of radioactivity was recovered in urine and feces, respectively, over a 96-hour period, demonstrating that the fecal route is the major excretion route. More than 90% of the recovered radioactivity had been eliminated by 48 hours post dosing. A similar pattern was noted in female rats. When ^{14}C-bromfenac was orally administered to male cynomolgus monkeys, 53.4% of radioactivity was recovered in the urine and 8.4% in the feces within 36 hours of administration, suggesting a difference in the main excretion route or rate between animal species. A similar excretion pattern to that seen in cynomolgus monkeys was found in male rhesus monkeys.

Following a single intravenous administration of ^{14}C-bromfenac (3 mg/kg) to cannulated male rats, 62.0% of the radioactivity was excreted into bile and 22.3% was excreted into the urine within 24 hours of dosing.

When ^{14}C-bromfenac was administered orally to lactating female rats at 2 weeks after delivery, radioactivity in milk accounted for 25% of the plasma radioactivity at 6 hours after dosing when maximum concentrations were present in milk. The radioactivity in milk and plasma disappeared rapidly.

Protein Binding
The *in vitro* plasma protein binding of ^{14}C-bromfenac was assessed using plasma from 6 mammalian species. At all concentrations, the plasma protein binding ratio was very high (>95%) in each species, showing a minor dose dependency. At a concentration of 1.4 μg/mL, the percent of free drug was 2.51, 0.48, 0.19, 0.41, 0.33, and 0.16, respectively, in mouse, rat, dog, cynomolgus monkey, rhesus monkey, and human plasma.

The *in vitro* affinity of bromfenac sodium for melanin was compared to that of procaine hydrochloride, which has a high affinity for melanin. At the highest concentration tested, binding of bromfenac sodium was about 16.4% of the amount observed with procaine hydrochloride.

In *in vivo* studies in rabbits, bromfenac is distributed to the pigment rich tissues of the eyes (iris, retina), and *in vitro* studies indicated that bromfenac has the binding affinity to melanin at 74 nmol/mg melanin. The phototoxicity potential of bromfenac was not studied in toxicology studies, as these findings are most likely to be of no biologically relevance or clinical significance.

MICROBIOLOGY

Not applicable.

TOXICOLOGY

No irritation, local or systemic toxic effects have been seen in nonclinical ocular studies even using exaggerated dosing regimens and/or more concentrated solutions than those used clinically. As with other NSAIDS, high systemic doses of bromfenac caused gastrointestinal toxicity, with the rat appearing to be the most sensitive species. Bromfenac gave no indication of genotoxicity or carcinogenicity and did not affect fertility in rats or cause fetal malformations in rats or rabbits; post-implantation loss and reduced pup growth rates might be associated with maternal toxicity.

Ocular Tolerability
Ocular toxicity studies conducted in rabbits are summarized in Table 4 below. Endpoints focused on ocular toxicity, using specialised methods including fundus photography, electroretinograms (ERG) and slit lamp examination with and without fluorescein, in addition to traditional histopathology.

Table 4: Ocular Toxicity Studies on Bromfenac in New Zealand White Rabbits

Report number	Dose regimen	Concentration	Results/Endpoints
3941202	16×2 drops, 30 min apart	0.1% degraded formulations	Very slight reversible corneal injuries
3970301	4×2 drops, 3 hr apart	0.1% fresh & degraded formulations	No evidence of ocular toxicity
	16×2 drops, 30 min apart	0.1% fresh & degraded formulations	Very slight but reversible damage in 1 or 2 animals in each group; no evidence of degradant effects
3910912	5 days, 1 drop, 6-8× daily	0.2%	No effect on corneal wound healing/repair
880509	4 wks., 2 drops, 9× daily	0.5 %	No evidence of ocular toxicity
POS00004	4 wks., 1 drop 1, 2 and 4× daily	0.18% w/o sulfite	Nontoxic and non-irritating; histology, clinical signs, bodyweight, necropsy all comparable to control
	4 wks., 1 drop 2, 4 and 8× daily	0.08% with sulfite	
9105	13 wks., 1 drop, 4× daily	0.1, 0.2, 0.4%	Ocular exam, clinical signs, food consumption, bodyweight, necropsy, clinical chemistry, hematology; histology, S & TEM. No evidence of toxicity.

S & TEM: scanning and transmission electron microscopy of the cornea

In summary, findings in all ocular studies were absent or sporadic, in which case they were reversible and usually considered to be procedural, i.e. due to the frequent daily instillations rather than due to bromfenac. Bromfenac did not affect corneal wound healing in rabbits. The effective maximal dosages achieved in these studies were approximately 9 to 64 times that obtained with bromfenac ophthalmic solution in the clinical situation on a per eye per day basis, and a multiple of 20-30 times greater than that on a unit body weight basis**.**

Acute and Long-term Toxicity

Acute and long-term toxicity studies using non-ocular routes are summarised in Tables 5 and 6, below.

Table 5: Acute Toxicity Studies on Bromfenac

Species, sex, report No.	Route	NOEL	MTD	LD_{50}	Findings
		mg/kg			
Rat ♂+♀, 9614	p.o.		12.5		GI ulceration, emaciation, decreased activity, pallor etc.
Rat ♂+♀, 9633*	p.o.		5		GI ulceration, emaciation, decreased activity, pallor etc.
Cynomolgus monkey ♂, 9609	p.o.	Not Determined	> 1000		Emesis at all dose levels, reduced food consumption plus GI bleeding in one animal at 1000 mg/kg

*Comparison of fresh and degraded, degraded material did not seem to contribute to toxicity

Table 6: Bromfenac Multi-dose and Long-term Toxicology

Species, sex, report No.	Route	Dosage mg/kg/day	Duration	MTD mg/kg/day	Findings
Rat ♂+♀, 9627	p.o.	1.5 and 2.5	maximum of 4 weeks	1.5	No ophthalmic changes; pallor, reversible GI lesions, ↓RBC, ↓Hb, ↓serum protein, ↑ spleen (extramedullary hematopoiesis)
Mouse, ♂+♀ 87-0426	p.o.	Max. 5 to 7.5	2 years	> 5: NOEL 1	Slightly ↓ b.w. gain in ♀; inconsistent fluctuations in hematological parameters may relate to NSAID activity; gastric ulceration, subacute inflammation, enlarged centrilobular nuclei in liver
Rat, ♂+♀ 83-0518	p.o.	0, 0.1, 0.5 & 2.5	13 weeks	0.5	No ophthalmic changes; 80% mortality in high dose group with changes in blood parameters consistent with observed GI inflammation & ulceration; NOEL 0.1 mg/kg/day
Rat, ♂+♀ 87-0437	p.o.	0, 0.05, 0.3 and 0.6	2 years	0.3	Mortalities slightly ↑ in high dose group; inflammation & GI lesions + kidney lesions at 0.3 & 0.6 mg/kg/day
Rhesus monkey, ♂+♀ 83-0647	p.o.	0, 15, 45 and 135	13 weeks	45	Emesis at 45 mg/kg, emesis & 1 mortality at 135 mg/kg; ↑ESR, mild to moderate enteritis and gastritis in high dose group
Cynomolgus monkey 87-0318	p.o.	0, 10, 30 and 90/3*	1 year	3	Dose-related emesis, diarrhea, weight loss and ↓appetite, ↓activity; 1♂ in the 30 mg/kg/day group with intestinal inflammation and peritonitis (considered treatment-related) died at week 13

* The high dose was reduced from 90 to 3 mg/kg/day after 6 weeks. Necrosis, open lesions and bleeding of the tail tip were noted for all groups. Deaths occurred at various points in the study: 1 ♀ in the control group, 1 ♀ at 10 mg/kg/day due to intussusception of the small intestine, another ♀ in this group due to unknown reasons.

Genotoxicity

Bromfenac did not show mutagenic potential in various mutagenicity studies, including the reverse mutation, chromosomal aberration, and micronucleus tests.

Carcinogenicity

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.

Reproduction and Development

Bromfenac did not cause fetal malformations in rats or rabbits or affect fertility in rats. Other effects, including post-implantation loss and reduced pup growth rates, might be associated with maternal toxicity.

Treatment of rats at oral doses 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 treatment-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. A summary of the reproduction and developmental studies are provided in Table 7**.**

Table 7: Bromfenac Reproductive and Perinatal Developmental Toxicology

Species, sex & study No.	Route	Dosage mg/kg/day	Duration	NOEL mg/kg/day	Findings
Rat ♂ 84-0003	p.o.	0, 0.06, 0.3, 0.9	60 days	0.9	no effect on fertility; no signs of toxicity
Rat ♀ 84-0003	p.o.	0, 0.06, 0.3, 0.9	14 days pre-mating to max. 14 days post-natal	0.06 & 0.3 [b]	↑post-implantation loss and some dystocia [a] with mortality at high dose; no effect on fertility
Rat ♀ 83-0551	p.o.	0, 0.06, 0.3, 0.9	Gestation day 6-15	0.9	No overt maternal toxicity; not teratogenic – no change in survival, growth or development of fetuses
Rabbit ♀ 83-0551	p.o.	0, 1, 2.5, 7.5	Gestation day 6-18	2.5	1 mortality in high dose group (GI hemorrhage); ↓maternal b.w. in mid & high dose groups; marginal non-significant ↑post-implantation loss & ↓viable fetuses in high dose group; no other dose-related effects
Rat♀ 83-0560	p.o.	0, 0.06, 0.3, 0.9	Gestation day 15 to lactation day 20	0.06 & 0.3 [b]	↓maternal survival with peritonitis & ulceration, ↓b.w., ↑stillbirths, ↓growth in offspring in high dose group; ↓b.w. in mid dose group. No increase in fetal deformities compared to control.

[a] Labor difficulties

[b] 0.06 for general toxic effects and 0.3 for reproductive effects

REFERENCE

[Pr]PROLENSA®, Topical Ophthalmic Solution 0.07 % w/v, Submission Control No: 238790, Product Monograph, Bausch & Lomb Incorporated, December 8, 2020.

PART III: CONSUMER INFORMATION

[Pr]Eugia-Bromfenac
Bromfenac Ophthalmic Solution
0.07 % w/v (as bromfenac sodium sesquihydrate)
Topical Ophthalmic Solution 0.07 % w/v

This leaflet is part III of a three-part "Product Monograph" published when Eugia-Bromfenac was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Eugia-Bromfenac. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Eugia-Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) used for treatment of pain and inflammation (swelling and redness) following cataract eye surgery.

What it does:
Eugia-Bromfenac eye drops work by reducing the production of certain substances (for example, prostaglandins) that cause inflammation and pain.

When it should not be used:
Eugia-Bromfenac should not be used if you are allergic (hypersensitive) to bromfenac, or any of its nonmedicinal ingredients (See What the nonmedicinal ingredients are), or to other nonsteroidal anti- inflammatory medicines such as acetylsalicylic acid, difusinal, fenoprofen, flurbiprofen, ketoprofen, indomethacin, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin.

Eugia-Bromfenac contains sodium sulfite, which may cause allergic- type reactions. Eugia-Bromfenac should not be used if you are allergic or sensitive to sulfite.

What the medicinal ingredient is:
Bromfenac sodium sesquihydrate

What the nonmedicinal ingredients are:
Benzalkonium chloride, boric acid, edetate disodium, povidone, sodium borate, sodium sulfite, tyloxapol, sodium hydroxide, sodium sulfite and water.

What dosage forms it comes in:
Eugia-Bromfenac 0.07% is supplied in a 5 mL opaque white LDPE container with white LDPE nozzle and gray HDPE cap with a tamper-evident ring of 3 mL for commercial sizes.

WARNINGS AND PRECAUTIONS

BEFORE you use Eugia-Bromfenac talk to your doctor or pharmacist if:

- you have an allergy or sensitivity to sodium sulfite
- you have any allergies to any medications
- you take any blood thinning medications, or if you have any bleeding problems, or if you bruise easily
- you are allergic to acetylsalicylic acid or to any other nonsteroidal anti-inflammatory drugs (NSAIDS)
- you wear contact lenses
- you are pregnant or intend to become pregnant
- you are breastfeeding or intend to breast-feed
- you have been recently had major ocular surgeries or repeated ocular surgeries within a short period of time,
- you have corneal problems, ocular surface diseases (e.g., dry eye syndrome)
- you suffer from diabetes mellitus or rheumatoid arthritis
- your vision is blurred after taking Eugia-Bromfenac, do not drive or operate machinery until your vision clears.

WHILE taking Eugia-Bromfenac talk to your doctor if:

- you are not getting relief, your symptoms worsen, or new eye problems develop.

Do not use Eugia-Bromfenac more than two weeks unless advised by your doctor. There is risk of corneal problems if ophthalmic nonsteroidal anti-inflammatory drugs such as Eugia-Bromfenac are used beyond 14 days after the surgery.

In rare cases, you may experience a flare-up of inflammation after you stop taking Eugia-Bromfenac, due to your cataract surgery. Your doctor may need to monitor your eyes for signs of macular oedema (a build up of fluid in the eye) after you stop taking Eugia-Bromfenac.

INTERACTIONS WITH THIS MEDICATION

No specific drug interaction studies have been done for Eugia-Bromfenac.

Tell your doctor or pharmacist if you are taking any blood-thinning medication.

PROPER USE OF THIS MEDICATION

Usual adult dose:

The day before cataract surgery, one drop of Eugia-Bromfenac ophthalmic solution should be applied to the affected eye. On the day of cataract surgery, and for up to 14 days after cataract surgery, one drop of Eugia-Bromfenac once daily should be applied to the affected eye. Follow your physician instructions.

If you are using other eye medicines as directed by your doctor, these medicines should be applied at least 5 minutes apart.

Proper Use:

Eugia-Bromfenac should not be applied while wearing contact lenses. Remove contact lenses prior to applying Eugia-Bromfenac. The preservative in Eugia-Bromfenac, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 15 minutes after applying Eugia-Bromfenac.

To minimise the chance of contamination of the content, replace the bottle cap immediately after use and avoid touching the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. A single bottle of Eugia-Bromfenac is used to treat only one eye.

Discard any unused eye drops 28 days after opening.

How to Use:

1. Wash your hands well with soap and water before you start.
2. Tilt your head back or lie down.
3. Pull down your eyelid to create a "pocket" between the eyelid and the eye. The drop will go in here.
4. Hold the bottle upside down, not touching the eye, and allow the drop to fall in the "pocket".
5. Let go of the eyelid, close the eye for about 30 seconds. Try not blink or squeeze your eyelids.
6. Put the cap (top) back on the bottle.
7. If a drop misses your eye, try again.

Overdose:

If you think you, or a person you are caring for, have taken too much Eugia-Bromfenac, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If a dose is missed, it should be applied as soon as possible.
Do not take 2 doses to make up for the missed dose.
If it is almost time for the next dose, the missed dose should be skipped, and you should go back to your regular dosing schedule.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The most common side effects experienced by patients taking Eugia-Bromfenac were inflammation of the eye and eye pain.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your healthcare professional		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	inflammation of the eye		√	
	eye pain		√	
	Macular oedema (swelling and build-up of fluid in the center of the retina): blurry vision, blurry or wavy vision near or in the center of your field of vision, colors may appear washed out or faded.		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

HOW TO STORE IT

Store at room temperature between 15ºC - 25ºC. Discard 28 days after opening.

Keep this medication out of the reach and sight of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about Eugia-Bromfenac:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website:

(https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website http://www.eugiapharma.com or by calling at 1-855-648-6681.

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