1. NAME OF THE MEDICINAL PRODUCT

Yellox 0.9 mg/ml eye drops solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 0.9 mg bromfenac (as sodium sesquihydrate).
One drop contains approximately 33 micrograms bromfenac.

Excipient(s) with known effect:
Each ml of solution contains 50 micrograms of benzalkonium chloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear yellow solution.
pH: 8.1-8.5; osmolality: 270-330 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Yellox is indicated in adults for the treatment of postoperative ocular inflammation following cataract extraction .

4.2 Posology and method of administration

Posology
Use in adults, including the elderly
The dose is one drop of Yellox in the affected eye(s) twice daily, beginning the next day after cataract surgery and continuing through the first 2 weeks of the postoperative period.

The treatment should not exceed 2 weeks as safety data beyond this is not available.

Hepatic and renal impairment
Yellox has not been studied in patients with hepatic disease or renal impairment.

Paediatric population
The safety and efficacy of bromfenac in paediatric patients has not been established. No data are available.

Method of administration
For ocular use.

If more than one topical ophtalmic medicinal product is being used, each one should be administered at least 5 minutes apart.

To prevent contamination of the dropper-tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper-tip of the bottle

4.3 Contraindications

Hypersensitivity to bromfenac or to any of the excipients listed in section 6.1, or to other non-steroidal anti-inflammatory medicinal products (NSAIDs).
Yellox is contraindicated in patients in whom attacks of asthma, urticaria or acute rhinitis are precipitated by acetylsalicylic acid or by other medicinal products with prostaglandin synthetase inhibiting activity.

4.4 Special warnings and precautions for use

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

Cross-sensitivity
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs. Therefore, treating individuals who have previously exhibited sensitivities to these medicinal products has to be avoided (see section 4.3).

Susceptible persons
In susceptible patients, continued use of topical NSAIDs, including bromfenac 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. Consequently in at risk patients concomitant use of ophthalmic corticosteroids with NSAIDs may lead to a higher risk of corneal adverse events.

Postmarketing experience
Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus and 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 reactions which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaema) in conjunction with ocular surgery. Yellox should be used with caution in patients with known bleeding tendencies or who are receiving other medicinal products which may prolong bleeding time.

It has been observed in rare cases that upon withdrawal of Yellox, a flare-up of the inflammatory response, e.g. in the form of macular oedema, due to the cataract operation may occur.

Ocular infection
An acute ocular infection may be masked by the topical use of anti-inflammatory medicinal products.

Use of contact lenses
In general, contact lens wear is not recommended during the postoperative period following cataract surgery. Therefore, patients should be advised not to wear contact lenses during treatment with Yellox.

Excipients
Benzalkonium chloride
This medicinal product contains 0.00185 mg benzalkonium chloride in each drop which is equivalent to 0.05 mg/ml.

Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Patients should remove contact lenses before using this medicinal product and put them back 15 minutes afterwards.

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised.

Patients should be monitored in case of prolonged use.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No interactions with antibiotic eye drops used in conjunction with surgery have been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of bromfenac in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Since the systemic exposure in non-pregnant women is negligible after treatment with Yellox, the risk during pregnancy could be considered low.

However, because of the known effects of prostaglandin biosynthesis-inhibiting medicinal products on the foetal cardiovascular system (closure of ductus arteriosus), the use of Yellox during third trimester pregnancy should be avoided. The use of Yellox is in general not recommended during pregnancy unless the benefit outweighs the potential risk.

Breast-feeding
It is unknown whether bromfenac or its metabolites are excreted in human milk. Animal studies have shown excretion of bromfenac in the milk of rats following very high oral doses (see section 5.3). No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman to bromfenac is negligible. Yellox can be used during breast-feeding.

Fertility
No effects of bromfenac on the fertility were observed in animal studies. In addition the systemic exposure to bromfenac is negligible; for this reason no pregnancy testing or contraceptive measures are required.

4.7 Effects on ability to drive and use machines

Yellox has minor influence on the ability to drive and use machines. Transient blurring of vision may occur on instillation. If blurred vision occurs at instillation patients should be advised to refrain from driving or using machines until vision is clear.

4.8 Undesirable effects

Summary of the safety profile
Based on clinical data available, a total of 3.4% of patients experienced one or more adverse reactions. The most common or most important reactions in the pooled studies were abnormal sensation in eye (0.5%), corneal erosion (mild or moderate) (0.4%), eye pruritus (0.4%), eye pain (0.3%) and eye redness (0.3%). Corneal adverse reactions were only observed in the Japanese population. Adverse reactions rarely led to withdrawal, with a total of 8 (0.8%) patients who prematurely discontinued treatment in a study due to an adverse reaction. These comprised 3 (0.3%) patients with mild corneal erosion, 2 (0.2%) patients with eyelid oedema and 1 (0.1%) patient each with abnormal sensation in eye, corneal oedema, or eye pruritus.

Tabulated list of adverse reactions
The following adverse reactions were classified according to the following convention: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000);

very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The table below describes adverse reactions by system organ class and frequency.

MedDRA system organ class	**Frequency**	**Adverse reactions**
Eye disorders	Uncommon	Visual acuity reduced Haemorrhagic retinopathy Corneal epithelium defect** Corneal erosion (mild or moderate) Corneal epithelium disorder Corneal oedema Retinal exudates Eye pain Eyelid bleeding Vision blurred Photophobia Eyelid oedema Eye discharge Eye pruritus Eye irritation Eye redness Conjunctival hyperaemia Abnormal sensation in eye Ocular discomfort
	Rare	Corneal perforation* Corneal ulcer* Corneal erosion, serious* Scleromalacia* Corneal infiltrates* Corneal disorder * Corneal scar*
Respiratory, thoracic and mediastinal disorders	Uncommon	Epistaxis Cough Nasal sinus drainage
	Rare	Asthma*
General disorders and administrative site conditions	Uncommon	Face swelling

*Serious reports from post-marketing experience of more than 20 million patients
** Observed with four times daily dose

Patients with evidence of corneal epithelial breakdown should be instructed to immediately discontinue use of Yellox and should be monitored closely for corneal health (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No abnormal findings or adverse reactions of clinical concern were noted upon administration of two drops 2mg/ml solution four times a day for the period of up to 28 days. Accidental administration of more than one drop should not result in increased topical exposure as excessive volume would rinse out of the eye due to limited conjunctival sac capacity.

There is practically no risk of adverse effects due to accidental oral ingestion. Ingestion of the 5 ml bottle content corresponds to an oral dose of less than 5 mg bromfenac, which is 30 times lower than daily dose of bromfenac oral formulation formerly used.
If Yellox is accidentally ingested, fluids should be taken to dilute the medicinal product.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophtalmologicals, Antiinflammatory agents, non-steroids, ATC code: S01BC11.

Mechanism of action
Bromfenac is a non-steroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity which is thought to be due to its ability to block prostaglandin synthesis by inhibiting primarily cyclooxygenase 2 (COX-2). Cyclooxygenase 1 (COX-1) is only inhibited to a small extent.
In vitro, bromfenac inhibited the synthesis of prostaglandins in the rabbit iris ciliary body. The IC50-values were lower for Bromfenac (1.1 μM) than for indometacin (4.2 μM) and pranoprofen (11.9 μM) Bromfenac at concentrations of 0.02%, 0.05%, 0.1% and 0.2% inhibited almost all signs of ocular inflammation in an experimental uveitis model in rabbits.

Clinical efficacy
Two Phase II multicentre, randomised, double-masked, parallel group studies were conducted in Japan, and two Phase III multicentre, randomised (2:1), double-masked, parallel group, placebo-controlled studies were conducted in the US to assess the clinical safety and efficacy of Yellox dosed twice daily in the treatment of post-operative inflammation in patients undergoing cataract surgery. In these studies, study substance was administered approximately 24 hours after cataract surgery and continued for up to 14 days. Treatment effect was evaluated up to 29 days.
A significantly greater proportion of patients in the Yellox group 64.0% vs. 43.3% in the placebo group ($p<0.0001$) experienced complete clearance of ocular inflammation at study day 15. There was significantly less anterior chamber cells and flare within the first 2 weeks post-surgery (85.1% of patients with flare score of ≤ 1) vs. placebo (52%). The difference in the rate of inflammation clearance showed as early as day 3.
In a large, well-controlled study that was conducted in Japan, Yellox was shown to be as effective as pranoprofen ophthalmic solution.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Yellox in all subsets of the paediatric population in postoperative ocular inflammation (see section 4.2 for information on paediatric use)

5.2 Pharmacokinetic properties

Absorption
Bromfenac efficiently permeates the cornea of cataract patients: A single dose resulted in a mean peak aqueous humour concentrations of 79±68 ng/ml at 150-180 minutes after dosing. Concentrations were maintained for 12 hours in aqueous humour with measurable levels up to 24 hours in major ocular tissues including the retina. Following twice daily dosing with bromfenac eye drops plasma concentrations were not quantifiable.

Distribution
Bromfenac shows high binding to plasma proteins. *In vitro*, the 99.8% were bound to proteins in human plasma.
No biological relevant melanin binding was observed *in vitro*.
Studies in rabbits using radio-labelled bromfenac have demonstrated that highest concentrations after topical administration are observed in the cornea followed by the conjunctiva and the aqueous humour. Only low concentrations were observed in the lens and vitreous.

Biotransformation
In vitro studies indicate that bromfenac is mainly metabolised by CYP2C9, which is absent in both iris-ciliary body and retina/choroid and the level of this enzyme in the cornea is less than 1% compared to the corresponding hepatic level.
In orally treated humans unchanged parent compound is the major component in plasma. Several conjugated and unconjugated metabolites have been identified with the cyclic amide being the major urinary metabolite.

Elimination
After ocular administration the half-life of bromfenac in aqueous humour is 1.4 h indicating rapid elimination.
After oral administration of 14C-bromfenac to healthy volunteers, urinary excretion was found to be the major route of radioactive excretions, accounting for approximately 82% while faecal excretion represented approximately 13% of the dose.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety, pharmacology, 'repeated-dose' toxicity, genotoxicity and carcinogenic potential. However, 0.9 mg/kg/day in rats at oral doses (900 times the recommended ophthalmic dose) caused embryo-foetal lethality, increased neonatal mortality, and reduced postnatal growth. Pregnant rabbits treated orally with 7.5 mg/kg/day (7500 times the recommended ophthalmic dose) caused increased post-implantation loss (see section 4.6).

Animal studies have shown excretion of bromfenac in breast milk when applied orally at doses of 2.35 mg/kg which is 2350 times the recommended ophthalmic dose. However, following ocular administration plasma levels were not detectable (see section 5.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid
Borax
Sodium sulphite, anhydrous (E221)
Tyloxapol
Povidone (K30)
Benzalkonium chloride
Disodium edetate
Water for injections
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.
After first opening: 4 weeks.

6.4 Special precautions for storage

Do not store above 25°C.
Patients should be instructed to keep the bottle tightly closed when not in use.

6.5 Nature and contents of container

5 ml solution in a polyethylene squeeze bottle with a dropper-tip and a polyethylene screw cap.
Pack of 1 bottle.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

BAUSCH + LOMB IRELAND LIMITED
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24PPT3
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/692/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18.05.2011
Date of latest renewal: 11.01.2016

10. DATE OF REVISION OF THE TEXT

04 February 2022

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu