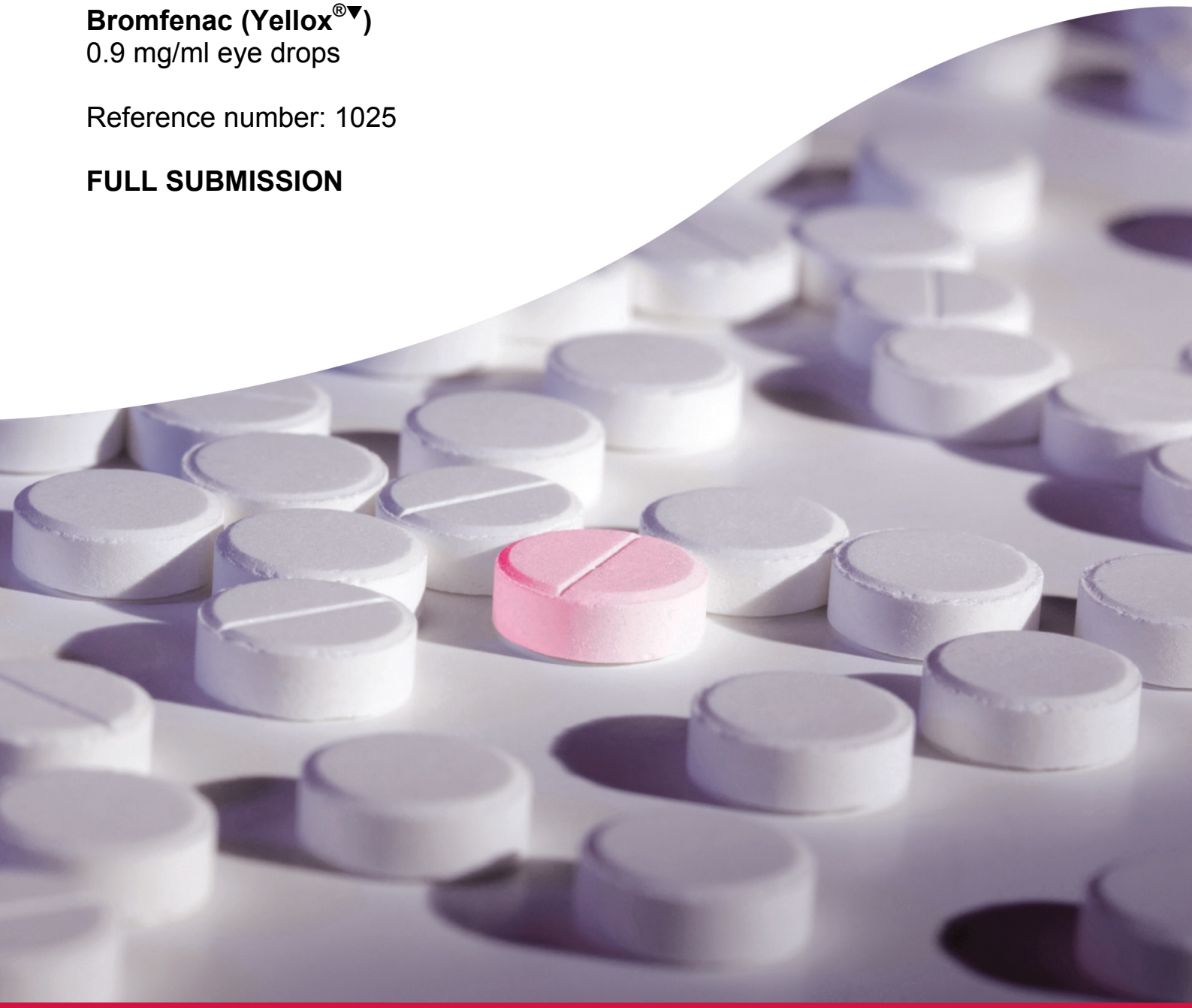
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Bromfenac (Yellox®▼)
0.9 mg/ml eye drops

Reference number: 1025

FULL SUBMISSION



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AWMSG Secretariat Assessment Report
Bromfenac (Yellox®▼) 0.9 mg/ml eye drops

This assessment report is based on evidence submitted by Bausch & Lomb UK Ltd on 19 September 2013[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Bromfenac (Yellox®▼) is indicated for the treatment of postoperative ocular inflammation following cataract extraction in adults[2].
Dosing	The dose is one drop of bromfenac in the affected eye(s) twice daily, beginning the next day after cataract surgery and continuing through the first two weeks of the postoperative period. The treatment should not exceed two weeks as safety data beyond this is not available[2].
Marketing authorisation date	18 May 2011[2]

2.0 DECISION CONTEXT

2.1 Background

Cataract is a common and important cause of visual impairment world-wide. The cause(s) for cataract are multifactorial and can include age, gender, diabetes mellitus, sunlight, steroids, nutrition, lifestyle and dehydration. Surgical removal of the cataract remains the only effective treatment available to restore or maintain vision[3]. Between 2010 and 2011, 17,120 patients in Wales underwent cataract surgery[4].

Postoperative inflammation following cataract surgery is a frequent condition, which can lead to significant complications in the anterior segment (iridocyclitis with miosis and pain, posterior synecchiae) or in the posterior pole of the eye. The postoperative inflammatory reaction that follows cataract surgery is usually mild; it may not be accompanied by classic signs of inflammation such as aqueous cells and flare, posterior synecchiae and cellular debris in the anterior chamber[5].

Treatment regimens to reduce postoperative inflammation include glucocorticoid eye drops, often in combination with a broad spectrum antibiotic. However, a significant number of patients develop postoperative complications, such as cystoid macular oedema. While corticosteroids can be effective in controlling inflammation, the ocular side effects of corticosteroids are well recognised[5]. Bromfenac is a NSAID that has anti-inflammatory activity which is thought to be due to its ability to block prostaglandin synthesis by primarily inhibiting cyclooxygenase 2 (COX-2); cyclooxygenase 1 (COX-1) is only inhibited to a small extent[2].

2.2 Comparators

The comparators included in the company submission were:

- Nepafenac (Nevanac®)
- Ketorolac trometamol (Acular®)
- Diclofenac (Voltarol Ophtha®)

2.3 Guidance and related advice

- Royal College of Ophthalmologists. Cataract surgery guidelines (2010)[3].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included details of two pivotal phase III trials, ISTA-BR-CS001-ER and ISTA-BR-CS001-WR, which assessed the efficacy and safety of bromfenac versus placebo. Due to their identical design, these trials will be described together; results will be presented as a pooled analysis. In addition, the company provided information on a comparative phase III trial, which investigated the efficacy of bromfenac versus pranoprofen; however, this study will not be discussed further as pranoprofen is not licensed in the UK. The company submission also included two phase II trials investigating dose concentration and frequency; however, these trials will not be discussed[1].

3.1 ISTA-BR-CS001-ER and ISTA-BR-CS001-WR

ISTA-BR-CS001-ER and ISTA-BR-CS001-WR were randomised, multicentre, double-masked, parallel, placebo-controlled phase III studies, which evaluated the efficacy and safety of bromfenac 0.1% ophthalmic solution in adult patients (≥ 18 years) who were scheduled for unilateral cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber intraocular lens implantation[1,5,6]. Patients were excluded from the study if they had received or were receiving anticoagulant therapy, corticosteroids, NSAIDs, antihistamines, mast cell stabilisers and unpreserved artificial tears. Patients (n = 527) were randomised 2:1 to receive bromfenac 0.1% ophthalmic solution (n = 356) or placebo (n = 171). Each patient self-administered a one drop dose of either bromfenac 0.1% ophthalmic solution or placebo, twice daily, beginning 16 to 32 hours after surgery and continuing for 14 days[1,5,6].

The primary endpoint was the proportion of patients in the intent-to-treat (ITT) group with cleared ocular inflammation in the study eye at visit four (day 15). Cleared ocular inflammation was defined as a summed ocular inflammation score (anterior chamber cell score plus flare score, each measured at a 5-point scale) of zero (refer to Appendix 1)[1,5,6].

In the pooled analysis, a higher proportion of bromfenac-treated patients (64.0%) than placebo-treated patients (43.3%) had experienced clearance of ocular inflammation at visit 4 (day 15); this was found to be statistically significant ($p < 0.0001$)[1,5,6]. Statistically significant treatment differences were also observed for the studies analysed separately[1,5]. Secondary endpoints included the proportion of pain-free patients, patients with a marked improvement in ocular inflammation, time to resolution of ocular pain, and the proportion of patients who discontinued treatment due to lack of efficacy. These were found to be supportive of the results obtained for the primary endpoint[5,6]. Refer to Table 1.

Table 1. Endpoint results for the pooled analysis and studies ISTA-BR-CS001-ER and ISTA-BR-CS001-WR[5,6]

	Bromfenac 0.1% ophthalmic solution	Placebo	p value
Pooled results	**n = 356**	**n = 171**	
Primary analysis: proportion of patients in the ITT group with cleared ocular inflammation in the study eye at visit four (day 15) (no censoring)*	228 (64.0%)	74 (43.3%)	< 0.0001
Primary analysis: proportion of patients in the ITT group with cleared ocular inflammation in the study eye at visit four (day 15) (test treatment only)	211 (59.3%)	46 (26.9%)	< 0.0001
Proportion of pain-free patients on study day 14	93.5%	69.6%	< 0.0001
Proportion of patients with a marked improvement in ocular inflammation on study day 15	303 (85.1%)	90 (52.6%)	< 0.0001
Median time to resolution of ocular pain (days)	2	5	< 0.0001
ISTA-BR-CS001-ER	**n = 198**	**n = 98**	
Primary analysis: proportion of patients in the ITT group with cleared ocular inflammation in the study eye at visit four (day 15) (no censoring)*	124 (62.6%)	39 (39.8%)	0.0002
Primary analysis: proportion of patients in the ITT group with cleared ocular inflammation in the study eye at visit four (day 15) (test treatment only)	113 (57.1%)	23 (23.5%)	< 0.0001
Median time to resolution of ocular pain (days)	2	4	< 0.0001
Proportion of patients who discontinued treatment due to lack of efficacy	6/198 (3.0%)	21/98 (21.4%)	< 0.0001
ISTA-BR-CS001-WR	**n = 158**	**n = 73**	
Primary analysis: proportion of patients in the ITT group with cleared ocular inflammation in the study eye at visit four (day 15) (no censoring)*	104 (65.8%)	35 (47.9%)	< 0.0099
Primary analysis: proportion of patients in the ITT group with cleared ocular inflammation in the study eye at visit four (day 15) (test treatment only)	98 (62.0%)	23 (31.5%)	< 0.0001
Median time to resolution of ocular pain (days)	2	5	< 0.0001
Proportion of patients who discontinued treatment due to lack of efficacy	5/158 (3.2%)	16/73 (21.9%)	0.0001

*For patients who prematurely discontinued test agent and were provided with an alternative anti-inflammatory medication, this analysis represents not only the test agent but also the rescue medication at visit 4.

ITT: intention-to-treat

3.2 Comparative safety

In the pivotal clinical trials, ISTA-BR-CS001-ER and ISTA-BR-CS001-WR, 356 patients were exposed to bromfenac 0.1% ophthalmic solution[6]. Of these, 6.7% of patients experienced one or more adverse events (AEs)[5]. The majority of AEs were reported for fewer patients in the bromfenac group than placebo group[6]. Frequently reported AEs included iritis (7.0% bromfenac group versus 18.1% placebo, p = 0.0001), eye pruritus (3.9% versus 2.9%) and eye irritation (2.5% versus 4.7%)[6].

Compared to the bromfenac group, a greater proportion of patients in the placebo group discontinued from the study due to AEs (3.1% versus 19.9%)[1,2,5].

3.2 AWTTC critique

- In their submission, the company included details of two pivotal placebo-controlled phase III trials, ISTA-BR-CS001-ER and ISTA-BR-CS001-WR[1]. No comparative evidence was provided.
- The company submission did not include efficacy or safety outcomes for bromfenac beyond 15 days[1]. The Summary of Product Characteristics (SPC) states that bromfenac treatment should not exceed two weeks as safety data is unavailable beyond this time point[2]. In comparison, nepafenac and ketorolac trometamol may be used for up to three weeks[7,8] and, diclofenac may be used for up to four weeks[9,10].
- In the pivotal trials, ISTA-BR-CS001-ER and ISTA-BR-CS001-WR, patients who prematurely discontinued treatment with bromfenac 0.1% ophthalmic solution or placebo were provided with an alternative anti-inflammatory medication. Therefore, the efficacy results reported in the pivotal trials accounted for patients who received not only bromfenac 0.1% ophthalmic solution but also rescue medication at study day 15[5].
- The pivotal trials included in the company submission were of double-blind design. However, a Good Clinical Practice inspection, requested by the Committee for Medicinal Products for Human Use (CHMP), revealed that the test products (bromfenac and placebo) were different in appearance. Therefore, the trials were not considered to be truly double-blinded. CHMP concluded that this possible unblinding had no effect on efficacy results as the endpoints relied on scores that were considered to be objective[5].
- CHMP highlighted that the time between the surgical procedure and the first application of medication, used in the clinical trials (16–32 hours), may not be optimal in the clinical setting. CHMP concluded that the initiation of therapy prior to surgery may have a beneficial effect on the treatment/prevention of inflammation; this has not been investigated[5].
- Bromfenac 0.9 mg/ml eye drops are administered twice-daily[2]. Other topical ophthalmic NSAIDs such as nepafenac, ketorolac trometamol and diclofenac are administered three and four times per day, respectively[7–10]. The company state that this twice-daily dosing may decrease corneal exposure to the active ingredients/preservatives, and may also aid compliance[1].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

In their submission, the applicant company state that they are not in a position to produce a full health economic evaluation and model[1]. Therefore, no information relating to the cost-effectiveness of bromfenac was provided.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

The budget impact evidence presented by the company included a comparison of the costs associated with the use of bromfenac, nepafenac and ketorolac trometamol for the treatment of postoperative ocular inflammation following cataract extraction in adults[1].

Using Welsh Health Statistic data, which stated that 17,120 patients underwent cataract surgery between 2010 and 2011, the company projected forward to estimate patient numbers for 2012–2013 and 2013–2014. Based on this projection, the company estimate that there would be approximately 17,000 patients undergoing cataract surgery between 2013 and 2014. Based on uptake figures of bromfenac in England of 9%, the company estimate that approximately 1,533 patients would receive treatment with bromfenac; this would lead to a total annual cost of £13,031[1].

5.2 AWTTC critique of the budget impact analysis

- Uptake figures were based on post-launch data for England[1]; this may therefore be subject to uncertainty.
- The company state that patients undergoing cataract surgery would be prescribed a steroid alone; NSAIDs, prescribed alongside a steroid, would be prescribed in high-risk patients (e.g. patients with diabetes, uveitis, age related macular deterioration, and those with a previous history of cystoid macular oedema[1].

5.3 Comparative unit costs

Table 2 provides information on comparative treatment acquisition costs of bromfenac (Yellox®▼), ketorolac trometamol (Acular®) and nepafenac (Nevanac®), diclofenac (Voltarol Optha®) and flurbiprofen (Ocufen®).

Table 2. Example comparative medicine acquisition costs for the treatment of postoperative ocular inflammation following cataract extraction in adult patients

Medicine	Example regimen*	Cost of treatment (£)**
Bromfenac (Yellox®▼) 5 ml	1 drop twice daily for two weeks	£8.50
Ketorolac trometamol (Acular®) 5 ml	1 drop three times daily for up to three weeks	£3.00
Nepafenac (Nevanac®) 5 ml	1 drop three times daily for up to three weeks	£14.92
Diclofenac (Voltarol Ophtha®) 5 ml	1 drop four times daily for up to four weeks	£6.68
Diclofenac (Voltarol Ophtha®) Single dose (40 doses)	1 drop four times daily for up to four weeks	£32
Flurbiprofen (Ocufen®) Single dose (10 x 4 unit dose)	1 drop every 30 minutes two hours before surgery. 1 drop four times daily for two to three weeks after surgery	£37.15

*Based on SPC dosing instruction [2,7–11].
**Costs are based on Monthly Index of Medical Specialities (MIMS) list prices as of October 2013[12].
This table does not imply therapeutic equivalence of medicines or the stated doses.
Refer to the SPCs for full dosing details[2,7–11]

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, bromfenac (Yellox®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company do not anticipate that bromfenac (Yellox®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 30 September 2013
Date range of evidence search: No date limits were applied to database searches.

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APPENDIX 1. Additional clinical information.

Table 1A. Anterior chamber cell counts and flare grade for determining the summed ocular inflammation score[5]

Anterior chamber cells		Anterior chamber flare	
0	0–5 (trace)	0	Complete absence
1	6–15	1	Very slight
2	16–25	2	Moderate
3	26–50	3	Marked
4	> 50	4	Intense