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EMA/431843/2011
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

**Yellox**

**(bromfenac)**

**Procedure No.: EMEA/H/C/001198**

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACP | Anterior chamber protein |
| ADRs | Adverse Drug Reactions |
| AE | Adverse Event |
| ASMF | Active Substance Master File |
| AST, ALT | Aspartate aminotransferase, Alanine aminotransferase |
| BAC | Benzalkonium chloride |
| BFSS | Bromfenac sodium sesquihydrate |
| BFSS-OS | Bromfenac sodium sesquihydrate ophthalmic solution |
| CHMP | Committee |
| COX | Cyclooxygenase |
| CRO | Contract Research Organisation |
| EC | European Commission |
| EMA | European Medicines Agency |
| ERG | Electroretinography |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| GMP | Good Manufacturing Practice |
| HPLC | High-performance liquid chromatography |
| IMP | Investigational Medicinal Product |
| INN | International Name |
| ITT | Intent-to-treat |
| LOCF | Last Observation Carried Forward |
| MAH | Marketing Authorisation Holder |
| NSAID | Nonsteroidal anti-inflammatory drugs |
| PGs | Prostaglandins |
| PK | Pharmacokinetics |
| POI | Postoperative inflammation |
| PSUR | Periodic Safety Update Report |
| RMP | Risk Management Plan |
| SARs | Serious Adverse Reactions |
| SmPC | Summary of Product Characteristics |
| TLC | Thin layer Chromatography |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Croma-Pharma GmbH submitted on 2 July 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Yellox, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 2 October 2007.

The applicant applied for the following indication: Treatment of postoperative ocular inflammation and pain.

**The legal basis for this application refers to:**

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

## *Information on Paediatric requirements*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMEA-000269-PIP01-08 on the granting of a product-specific waiver for the following conditions:

- Postoperative ocular inflammation
- Paediatric subsets: All subsets of the paediatric population from birth to less than 18 of age for eye drops, solution for ocular use

On the grounds that the specific medicinal product does not represent a significant therapeutic benefit as the needs are already covered.

## *Information relating to orphan market exclusivity*

**Similarity**

Not applicable.

**Market Exclusivity**

Not applicable.

## *Scientific Advice:*

The applicant did not seek scientific advice at the CHMP.

## *Licensing status*

The product was not licensed in any country at the time of submission of the application.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jens Heisterberg

Co-Rapporteur: Tomas Salmonson

- The application was received by the EMA on 2 July 2009.
- The procedure started on 22 July 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 October 2009 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 October 2009.
- During the meeting on 16-19 November 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 November 2009.
- A GCP inspection was carried out at two investigator sites in USA (13-15 April 2010 and 9-10 April 2010) and at the sponsor site (18-20 May 20100), in relation to the conduct of trial ISTA-BR-CS001. The final integrated inspection report was issued on 15 July 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 May 2010.
- The Rapporteurs circulated the Joint Assessment Reports on the applicant’s responses to the List of Questions to all CHMP members on 5 July 2010 and 7 July 2010.
- During the CHMP meeting on 19-22 July 2010 the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 August 2010.
- The Rapporteurs circulated the Joint Assessment Reports on the applicant’s responses to the List of Outstanding Issues on 08 September 2010.
- During the CHMP meeting on 20-23 September 2010 the CHMP agreed on the second List of Outstanding Issues to be addressed in writing by the applicant.
- A further GCP inspection was carried out at the two involved CRO sites (25-28 October 2010). The final integrated inspection report was issued on 10 January 2011.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 14 February 2011.
- The Rapporteurs circulated the Joint Assessment Reports on the applicant’s revised responses to the second List of Outstanding Issues to all CHMP members on 03 March 2011.
- During the meeting on 17 March 20111, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Yellox on 17 March 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 16 March 2011.

# 2. Scientific discussion

## *2.1. Introduction*

Postoperative inflammation following cataract surgery is a frequent, possibly unavoidable 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, notably the Irvine-Gass syndrome, which is also known as pseudophakic cystoid macular oedema, although it can be seen also after cataract surgery without implantation of an artificial intraocular lens. Topical anti-inflammatory is routinely used by some ophthalmologists to avoid such complications.

The postoperative inflammatory reaction that follows uneventful cataract surgery is usually rather mild and may be devoid of classic signs of inflammation such as aqueous cells and flare, posterior synecchiae and cellular debris in the anterior chamber, for which a potent mydriatic in combination with topical or systemic glucocorticoid treatment is mandated. Despite being inconspicuous upon slit-lamp biomicroscopic examination, the inflammation may be severe enough, however, to produce pseudophakic cystoid oedema. This reaction is believed to be mediated by prostaglandins released in the anterior segment. Thus, the essential pathophysiological stimulus of the inflammation appears to be the surgical trauma, although a potential role of an infectious agent cannot be ruled out, hypothetically being masked by the routine use of prophylactic antibiotics during and after cataract surgery. The rate of culture-positive endophthalmitis following cataract surgery is vastly inferior to that of pseudophakic cystoid macular oedema.

A typical postoperative regimen to reduce the inflammation after cataract surgery includes glucocorticoid eye drops instillation for one to three weeks, often in combination with a broad spectrum antibiotic. Although usual care comprises such anti-inflammatory treatment, a significant number of patients develop postoperative complications such as cystoid macular oedema due to an insufficiently controlled inflammation. While corticosteroids are quite effective in controlling inflammation, the ocular side effects of corticosteroids are well recognised. Not only are there patients who are known to respond to topical glucocorticoids with intraocular pressure elevation, but the average cataract patient has not previously been exposed to topical glucocorticoids and therefore cannot be known not to respond with pressure elevation. Consequently, nonsteroidal anti-inflammatory drugs provide surgeons with an alternative therapy for the reduction of inflammation after cataract surgery. Indeed, some surgeons prefer to use a topical NSAID as the first choice of topical postoperative anti-inflammatory treatment.

Bromfenac sodium sesquihydrate (BFSS) was originally developed by Wyeth-Ayerst as an oral formulation for short-term systemic use and approved in the USA (Duract capsules). Subsequently, hepatotoxicity associated with high doses (25-100 mg) and long-term use of bromfenac, was observed in some users of the drug. The drug was voluntarily withdrawn from the market in June 1998.

Bromfenac sodium sesquihydrate ophthalmic solution (BFSS-OS) is authorised and marketed in Japan as Bronuck (Senju Pharmaceutical Co Ltd) for ocular inflammatory disease and postoperative inflammation and in the US as Xibrom (ISTA Pharmaceuticals Inc) for the treatment of post-operative ocular inflammation following cataract extraction.

The formulation in Yellox was adapted to comply with the Ph.Eur requirements since the original formulation of BFSS-OS does not fulfil the limits for the Ph.Eur. test "5.1.3. Efficacy of antimicrobial preservation". Therefore, 0.15% polysorbate 80, used in the original formulation, has been replaced by 0.02% tyloxapol. This change made it possible to reduce the amount of benzalkonium chloride (BAK) from 0.005% to 0.003%.

Based on the CHMP questioning if the reduction of BAK from 0.005% to 0.003% could impact the efficacy of the product planned for the market, the BAK concentration has been raised to a level of 0.005% as in the tested solution used in the pivotal trials. Thus only minor differences, i.e. the exchange of polysorbate 80 to tyloxapol remain.

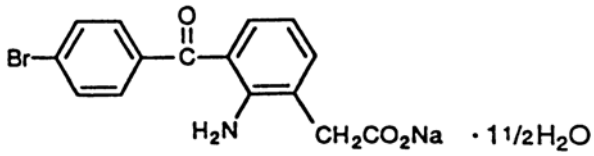
## *2.2. Quality aspects*

### 2.2.1. Introduction

Yellox eye drops, is a yellow sterile eye drops solution packaged in 5 ml transparent bottles containing 5 ml drug product. The eye drops solution contains bromfenac sodium sesquihydrate 1 mg/ml (nominally 0.1% (w/w) bromfenac sodium sesquihydrate, equivalent to 0.09% (w/w) of the free acid bromfenac). A single drop of the drug product contains about 33 µg of bromfenac.

### 2.2.2. Active Substance

The INN name of the active substance is bromfenac. Its chemical name is sodium[2-amino-3-(4-bromobenzoyl)phenyl] acetate sesquihydrate. The molecular formula of active substance is C15H11BrNNaO3 1½H2O. Its relative molecular mass is 383.17 and its structural formula is shown below.




Bromfenac sodium is a yellow to orange non-hygroscopic crystalline powder, freely soluble in water and slightly soluble in ethanol. Its pKa-value is 4.29. There is no evidence of polymorphism associated with bromfenac sodium.

#### *Manufacture*

An ASMF has been submitted for the active substance. A detailed description of the manufacturing process and process controls is provided. The manufacturing process development has been thoroughly described, critical parameters are identified and the critical steps are adequately described and controlled. Specifications for raw materials, starting materials, solvents, reagents, catalysts materials used in the synthesis are provided and the control is appropriate.

#### *Specification*

The drug substance specification includes tests for appearance (visual), colour, clarity and degree of opalescence of solution (Ph.Eur.), identification (active substance: FT-IR, HPLC; sodium: Ph.Eur.), pH (Ph.Eur.), heavy metals (Ph.Eur.), water content (Ph.Eur.), assay (HPLC), purity (HPLC), impurities (HPLC), residual solvents (GC) and microbial contamination (Ph.Eur.).

The active substance specification has been justified and is considered appropriate to ensure the quality of the active substance.

Batch analysis results from nine production batches covering the proposed batch range have been provided. All results are within the specification limits.

### *Stability*

Ten batches of bromfenac sodium manufactured by the proposed manufacturer were subjected to long-term stability testing at 25°C/60% RH and accelerated testing at 40°C/75% RH. Results were presented for up to 48 months long-term and for six months in accelerated conditions. Results from another three full scale batches have been presented for up to six months at both conditions.

All results are within the specification limits. No trends have been observed.

Photostability testing according to "Note for Guidance on Photostability Testing of New Active Substances and Medicinal Products" was carried out. Results indicate a slight degradation of the sample exposed to light. It is however confirmed that the container closure system provides suitable protection during storage of bromfenac sodium.

Based on the overall results the proposed retest period and storage conditions are accepted.

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

## 2.2.3. Finished Medicinal Product

### *Pharmaceutical Development*

Bromfenac sodium sesquihydrate 0.1% eye drops, solution is currently marketed in Japan and the U.S.A.

Solubility studies showed that bromfenac is significantly soluble and stable in pH values above 7 which was the most relevant factor leading to the final drug product formulation. The active substance is readily soluble in water making it a suitable active ingredient for an ophthalmic solution. Because of its aqueous solubility particle size is not a critical parameter.

Generally the excipients contained and their concentrations in the proposed formulation are typical for ophthalmic formulations. The proposed formulation is similar to the formulation already marketed in Japan and the U.S.A, with the difference of the solubilising agent.

Boric acid and sodium borate were chosen as the buffer system due to good buffer characteristics in the chosen range of pH. Sodium sulphite anhydrous is added as antioxidant, with the aim of suppressing the degradation of bromfenac. Benzalkonium chloride (BAC) is commonly used in ophthalmic formulations and was selected as preservative.

No compatibility problems with regard to excipients were observed during the stability results.

The choice of sterilisation procedure for the finished product has been justified.

The ingredients are added in a predefined order to water for injection, while mixing to ensure full dissolution. The manufacturing process has been optimised with respect to minimising the risk of degradation of bromfenac. The manufacturing equipment has been chosen with a view to minimise possible interaction with excipients and appropriate measures were put in place. The bio-burden is sufficiently monitored through the manufacturing process.

Yellox is filled into sterile 5 ml transparent bottles without additives. This material complies with Ph.Eur 3.1.3 and 3.1.4. The container closure system and the label materials were selected based on the results from the already marketed product in the U.S.A. They were also selected as they are

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

successfully and widely used for current marketed ophthalmic sterile solutions. The compatibility of the drug product with the selected closure system was shown by the stability results. The adhesive used in the labels complies with EU directives 1935/2004, 2002/72/EC and 85/572/EWG. Migration from the packaging material and label has been investigated and it is demonstrated that there is no relevant migration of container or label components into the formulation.

## *Adventitious agents*

No excipients of animal or human origin are used.

## *Manufacture of the product*

The general manufacturing process is typical for aqueous ophthalmic solutions. The ingredients are added in a predefined order to water for injection, while mixing to ensure full dissolution. Critical steps have been identified and appropriate in-process controls and acceptance criteria have been laid down.

Validation of the manufacturing process for Yellox eye drops, solution was performed on two pilot and three industrial scale batches manufactured by one of the proposed manufacturer and on three industrial batches manufactured by the second manufacturer.

The manufacturing process has been successfully validated. These data were provided in the response to the D120 CHMP List of Questions.

The results of successful media fill testing carried out at both finished product manufacturing sites were presented.

## *Product specification*

The release and shelf-life specifications include tests and limits for appearance (clarity and colour Ph.Eur.), container appearance (visual), particulate matter (Ph.Eur.), pH (Ph.Eur.), osmolality (Ph.Eur.), recovery volume (volumetric), identification (HPLC), assay (HPLC), impurities (HPLC), sodium sulphite assay (ion chromatography), BAC assay (HPLC), EDTA assay (HPLC), sterility (Ph.Eur.) and antimicrobial effectiveness test (Ph.Eur.).

Batch analysis results from two development batches and from the eight validation batches were provided. All results were within the specification limits except for assay of benzalkonium chloride for one batch however this has been adequately justified.

## *Stability of the product*

Preliminary stability studies have been performed up to 24 months at 25±2°C/40%±5% RH, 25±2°C/60%±5% RH, up to 12 months at 30±2°C/65%±5% RH and up to 6 months at 40±2°C/020%±5% RH. Two development batches and eight validation bathes manufactured by the two proposed manufacturers have been studied.

An unknown impurity was observed during stability testing but it has not been finally identified. It is likely not bromfenac related. Based on a non-clinical study an appropriate shelf-life limit for this impurity has been set considering the level seen in the long term stability studies on commercial scale batches. However, the applicant should continue the identification attempts of this unknown impurity. Should any structural elements of toxicological concern arise from the identification of this impurity, this has to be taken into account by the applicant, and the European Medicines Agency has to be informed accordingly.

All other tested parameters are within the specification limits and no trends are seen except for a decrease in sodium sulphite, which is acceptable.

A photostability study according to ICH guideline was performed on the drug product and it is shown that the drug product does not need to be protected from light and therefore transparent containers are suitable.

*In-use stability*

An in-use stability study has been performed with two newly manufactured batches of the drug product over a period of four weeks. The study simulated the pattern of the daily use of the drug product. A complementary in-use stability study will be performed with samples at the end of shelf-life, when available.

No changes were observed after opening the bottle and simulating the use of the drug product for 28 days (4 weeks). Hence, the drug product is considered to be stable for four weeks after first opening.

Based on the overall stability results the proposed shelf-life and storage conditions as well as the proposed in-use stability are considered acceptable.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Yellox eye drops solution is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. At the time of the CHMP opinion, there was a quality issue that will be addressed as Follow-up Measure within an agreed timeframe. This issue relates to identifying an unknown impurity observed during stability studies. However, this issue is not expected to have a negative impact on the Benefit Risk balance of the product.

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[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

To support the marketing authorisation application, the applicant has submitted the study reports from the non-clinical studies conducted by Senju Pharmaceuticals and Wyeth-Ayerst. To confirm that the changes in formulation do not impact the safety profile of the eye drop solution, the applicant has conducted non-clinical bridging studies: a 2-week ocular distribution study in rabbits (Study CRO28), a 4-week repeat-dose toxicity study in rabbits (Study CRO27), and an in vitro phototoxicity study (Study GPT 100313).

### 2.3.2. Pharmacology

Bromfenac is a well known non-steroidal anti-inflammatory drug (NSAID). The basic mechanism of action along with anti-inflammatory, anti-pyretic, and analgesic effects of bromfenac were examined in earlier studies performed by Wyeth-Ayerst using various *in vitro* techniques and *in vivo* models. The pharmacological basis of bromfenac's efficacy in ophthalmic use was examined by Senju Pharmaceuticals and these data have been supplemented by published data. The safety pharmacology of bromfenac sodium was evaluated by Wyeth-Ayerst in a battery of standard tests following oral and i.v. dosing in several species.

#### *Primary pharmacodynamic studies*

NSAIDs produce anti-inflammatory and analgesic effects by inhibiting the activity of cyclooxygenase (COX) enzymes that catalyse the conversion of arachidonic acid to prostaglandins. Prostaglandins (PGs) mediate many forms of systemic and localized inflammation including inflammation in ocular tissues. In animal models, PGs have been shown to produce disruption of the blood-aqueous humour barrier, vasodilatation, increased vascular permeability, and leukocytosis (Oka et al. 2004; Guex-Crosier 2001).

Bromfenac is a potent inhibitor of recombinant human COX-2 ($IC_{50}$ of 0.0066 µM) with a lower inhibiting activity towards COX-1 (0.21 µM). Ophthalmic bromfenac treatment (0.02-0.2% b.i.d. or q.i.d.) inhibited experimentally induced uveitis in male rabbits. Moreover, bromfenac inhibited prostaglandin synthesis in rabbit iris ciliary body *ex vivo* with an $IC_{50}$ of 1.1 µM. Bromfenac eye drops (0.02-0.2%) reduced the conjunctival oedema in rats resulting from local injection of arachidonic acid or carrageenan with up to 45%. Furthermore, bromfenac exerted an inhibitory effect on the trauma (paracentesis and laser irradiation) induced ocular inflammation. Hence, bromfenac (≥0.005%) suppressed prostaglandin E2 induced breakdown of the blood–aqueous barrier and the concomitant increase in aqueous humour protein concentration in rabbits. Similarly, bromfenac (0.09%) pre-treatment resulted in near complete inhibition (>95%) of i.v. LPS-induced increases in FITC-dextran and prostaglandin E2 concentrations in the anterior chamber and aqueous humour, respectively.

#### *Secondary pharmacodynamic studies*

Bromfenac did not affect the *in vivo* epithelial wound healing of the rabbit cornea. The potential for bromfenac to bind to secondary enzymes, receptors or ion channels has not been evaluated. In addition, no evaluation of potential effects on intraocular pressure and retinal functioning (ERG) has been conducted. Considering the topical ocular administration and the accumulated clinical experience

with ophthalmic bromfenac, the lack of an *in vitro* binding assay was considered acceptable by the CHMP.

### *Safety pharmacology programme*

Bromfenac's effect on the core organs was investigated in safety pharmacology studies applying p.o. and i.v. dosing. An analgesic effect was observed in mice at p.o. doses ≥ 3 mg/kg. No effect was observed on the gastrointestinal tract while increased blood pressure was seen in anaesthetized Beagle dogs i.v. administered 10 mg/kg bromfenac. Moreover, a decrease in urinary volume and in the $Na^+$ and $Cl^-$ ions excreted was detected in rats p.o. administered bromfenac doses ≥ 1 mg/kg. Considering that ocular administered bromfenac is not expected to reach the systemic circulation to a significant extent, the results from these studies were considered of limited relevance for the present indication.

### *Pharmacodynamic drug interactions*

No non-clinical studies were considered necessary to address this aspect.

## 2.3.3. Pharmacokinetics

### *Methods of analysis*

No validation reports for the methods of analysis have been submitted. A pivotal study for the present application is the ocular distribution study CRO28. Validation of the LC/MS/MS method has been performed. The quality of the validation report although not GLP compliant was acceptable.

### *Absorption*

Bromfenac-related radioactivity was detected in plasma following instillation into the conjunctival sac of male Japanese rabbits at a dose of 0.1 mg (0.05 mg/eye). $T_{max}$ occurred 30 minutes post-dosing and the calculated half-life was 2.2 hours.

The systemic absorption of bromfenac was investigated in mice, rats and monkeys following ocular, oral and i.v. administration. The terminal plasma half-life was 1.2 hours, 3.6-10 hours, 4.3-6.4 hours and 1-1.2 hours in mice, rats, rhesus monkeys and cynomolgus monkeys, respectively. The half-life in rats varied depending on whether bromfenac was administered to rats in a fed or fasted state. The oral bioavailability in cynomolgus monkeys was 45% following intragastric administration of bromfenac. No further non-clinical pharmacokinetic absorption studies were deemed necessary.

### *Distribution*

Bridging data between the "old" bromfenac formulation (Bronuck/Xibrom) were provided in study CRO 28 that compared the concentration of 0.1% bromfenac in the ocular tissues (lens, cornea, vitreous and aqueous humour) of pigmented Chinchilla Bastard rabbits (n=7 males/group) following repeated ocular administration of Bronuck and Yellox bromfenac formulations. Both eyes of the rabbits were instilled with a drop corresponding to 0.05 mg bromfenac/eye BID for 14 consecutive days.

This study was inconclusive as the following main deficiencies were identified:

- The sensitivity of the analytical method was insufficient since too many of the samples (28/54) from bromfenac-treated animals were below the method's limit of quantification or detection;

- Sampling of tissues/aqueous humour was made after 20 minutes when the maximal intraocular levels of bromfenac would have been expected after 30 minutes – 2 hours.

- No bromfenac absorption into the aqueous humour could be demonstrated for Yellox while bromfenac concentrations were determined in 3/7 animals receiving the Bronuck formulation. This last issue was solved by the applicant by increasing the BAC content to 0.5 %, identical to the BAK content in the marketed formulation.

To further substantiate the data set on comparability of the both formulations, an additional comparative GLP study in rabbit with single topical administration in the eye was performed. This study clearly showed that the bioavailability of the two formulations was similar.

Bromfenac had a moderate affinity to melanin but distribution studies in pigmented rats did not suggest any retention in pigmented tissues (e.g. the eyes). Following oral and i.v. administration, bromfenac distributed well throughout the body and high amounts were found in the liver and GI-tract of rats. Radioactivity was observed in foetal placenta and plasma following oral administration to pregnant rats although the levels were lower than that observed in the dams. Bromfenac showed high plasma protein binding in all species (>97%) and the plasma free fraction seemed to slightly increase with the plasma concentration in rats, monkeys and humans.

### *Metabolism*

CYP2C9 was identified as the principal enzyme responsible for bromfenac metabolism *in vitro* (only CYP1A2, CYP2C9*1/2, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 were evaluated).

The *in vivo* metabolism of bromfenac appeared to differ between rats, rabbits and monkeys. Following ocular administration of bromfenac, the parent compound and the metabolites AHR-10240, AHR-11652, AHR-11665, WAY-127039 were detected in rabbit aqueous humour and plasma. Based on non-clinical studies conducted with these metabolites, they are expected to possess a significantly lower pharmacodynamic activity as well as toxic potential than bromfenac. In addition, three unidentified metabolites constituted less than 2% of total plasma reactivity were detected in rabbit plasma. Following oral administration of 14C-bromfenac, AHR-11665 was the only metabolite detected in rat plasma. In rat urine, two additional metabolites were identified. AHR-11665 and AHR-10240 were also noted in rat bile. Only unchanged bromfenac was detected in the plasma of rhesus monkeys, orally and i.v. administered 14C-bromfenac. However, bromfenac and four metabolites were identified in the urine. Plasma metabolites were not evaluated in cynomolgus monkeys but five metabolites were detection in the urine; two pair of glucuronide conjugates and the cyclic amide AHR-10240.

The *in vivo* metabolism of bromfenac has not been investigated in mice. Moreover, it has not been studied in humans.

However, based on data from human liver microsomes and human liver microsomes expressing CYP450 cDNA, AHR-10240, AHR-11652, AHR-11665 and WAY-127039 may be formed in humans. In addition, two unidentified metabolites denoted M1 and M2 were detected. M2 was found to be the main human metabolite with a M2/parent compound ratio around 1/8. The structure of M2 has not been characterized. M2 does not appear to be formed in the animal species applied in the toxicology studies. Accordingly, the applicant was requested to discuss the validity of the performed genotoxicity and reproductive toxicity studies. The applicant stated that Bromfenac was only to a minor extent metabolised in the eye due to low expression of CYP 2C9, and therefore the human systemic exposure to M2 would be negligible and the non-clinical species, predictive of reproductive- and genetic toxicity. It was acknowledged by the Committee that the risk of toxicity related to systemic exposure of the M2 metabolite was low.

In a discussion on any potential for pharmacokinetic interactions due to concomitant or subsequent administration of other ocular drugs, the applicant stated that drugs usually co-administrated were not

substrates of CYP2C9; furthermore it was highlighted that Bromfenac was not an inhibitor of major cytochrome enzymes and that no interactions of Bromfenac with other drugs had been recorded in the clinical or post-marketing phases.

The CHMP acknowledged that interaction of Bromfenac with other drugs was not likely.

### *Excretion*

Approximately 20-50% of the dose was excreted via the urine in both rats and monkeys following PO and IV administration. In rats, approximately 40-60% of the dose was excreted via the bile. Much lower amount of bromfenac-related radioactivity was obtained in monkeys (4-22%). However, the recovery in these studies was also significantly lower (approximately 60% vs. 90% in rats and monkeys, respectively).

Bromfenac was detected in milk from lactating rats in levels similar or lower than that observed in the dams.

## 2.3.4. Toxicology

### *Single dose toxicity*

A single PO administration of bromfenac caused haemorrhagic injury of the GI tract in rats at doses ≥12.5 mg/kg. Mortalities were observed in 25 mg/kg. Findings in cynomolgus monkeys administered up to 1000 mg/kg consisted of vomiting and reduced food consumption. One 1000 mg/kg animal showed evidence of GI bleeding.

### *Repeat dose toxicity*

The pivotal 4-week repeat-dose toxicity study compared the effects following administration of Yellox and the "old" ophthalmic 0.1% bromfenac formulations (Bronuck/Xibrom). One drop (30 µL) of vehicle or test substance was administered into the conjunctival sac of the right eye of each rabbit. The animals were evaluated with respect to clinical signs, slit lamp ocular observation following instillation of fluorescein, ocular observation according to the Draize scoring system, body weight, food consumption, haematology and clinical biochemistry, necropsy and histopathology of both eyes. No findings were made in any of the treatment groups; hence the NOAEL was four drops Yellox per eye per day (0.12 mg bromfenac/eye/day).

However, the slit lamp and histopathology results were only reported as two very laconic tables in the report, which was considered unacceptable. The applicant supplied additional animal data, and although data in existing sub-reports from the involved experts still lacked details, no further documentation was deemed necessary.

A comprehensive ocular toxicity programme, comprising repeat dosing for up to 13 weeks with up to five times the clinical and increased instillation frequency, was conducted by Senju using the 'old' formulation of bromfenac sodium. Follow-up was concentrated on ocular toxicity, using specialised methods, such as fundus photography, ERG and slit lamp examination with and without fluorescein, in addition to traditional histopathology. The findings were sparse and discrete, mainly lesions to the corneal epithelium and mild eosinophilia and hyperplasia of lymph nodes adjacent to the corneal epithelium, after very frequent instillations. As such findings were present also in the control group they were considered to be due to the frequent instillations rather than to bromfenac.

Oral administration of bromfenac caused gastrointestinal toxicity in rats, rhesus and cynomolgus monkeys. The ulcerogenic effect of NSAIDs on the GI tract is well-described in the literature.

### *Genotoxicity and carcinogenicity*

Bromfenac was negative in a standard battery of genotoxicity tests.

In line with ICH S1A, carcinogenicity studies are not warranted for Yellox, since it will be indicated for a treatment period of only two weeks, and there is no special concern regarding carcinogenic potential. Still, long-term oral carcinogenicity studies showed that bromfenac had no carcinogenic potential in mice at doses up to 5 mg/kg/day and in rats at doses up to 0.6 mg/kg/day ish.

### *Reproduction Toxicity*

Orally administered bromfenac did not affect the fertility of male rats administered up to 0.9 mg/kg/day bromfenac (900 times the recommended ophthalmic dose). A reduction in total implantations and an increased incidence of post-implantation losses was observed at doses ≥0.3 mg/kg/day in rats. A slight increase in the percent of post-implantation loss was also observed in rabbits administered 7.5 mg/kg/day bromfenac (7500 times the recommended ophthalmic dose) from gestation day 6 to 18 PO. Bromfenac treatment during embryo-foetal development had no effect on sex ratio, and external, visceral and skeletal findings in neither rats nor rabbits. In the oral rat pre- and post-natal development study, no changes were observed in gestation length, delivery processes, nursing behaviours and viability of the newborn pups in any group. However, pup survival was reduced in the group receiving 0.9 mg/kg/day. Hence, the NOAEL was 0.3 mg/kg/day for the F1 pups.

### *Toxicokinetic data*

Toxicokinetic measurements were not included in either the oral repeat-dose toxicity, carcinogenicity or the reproductive toxicity studies. However, these toxicity studies were conducted prior to the release of the ICH S3A guideline which requests the inclusion of toxicokinetic measurements in pivotal toxicity studies. Nevertheless, judged on the clinical signs and reported adverse findings sufficient systemic exposure was obtained in the toxicity studies.

### *Other toxicity studies*

#### Phototoxicity

In vitro results obtained in Balb/c 3T3 cells showed that bromfenac did not possess a phototoxic potential.

## 2.3.5. Ecotoxicity/environmental risk assessment

The Applicant has submitted en environmental risk assessment (ERA), concluding that log Kow for bromfenac was below 4.5 at pH ≥ 4 (with rapid decomposition under more acidic conditions) and the predicted PECsurface water was lower than the threshold (0.01 µg/L).

Within a pH range of approximately 5 to 13, the log Kow did not exceed a value of 1.6. No further screening for persistence, bioaccumulation and toxicity was therefore considered necessary.

Altogether, it was considered that ocular treatment with Yellox would not pose a risk to the environment.

## 2.3.6. Discussion on non-clinical aspects

The non-clinical data did not reveal any special hazard for human based on conventional studies of safety, pharmacology, repeated-dose toxicity, genotoxicity and carcinogenicity potential. However,

studies in animals showed reproductive toxicity. The potential risk in human is unknown but since the systemic exposure in non-pregnant women is negligible after treatment with Yellox, the risk during pregnancy is considered low. However, because of the known effects of prostaglandin biosynthesis-inhibiting medicinal products on the foetal cardiovascular system, the use of bromfenac during pregnancy should be avoided.

Animal studies have also showed that bromfenac was excreted in breast milk when applied orally at high doses. However, following ocular administration, plasma levels were not detectable.

It is unknown whether bromfenac is excreted in human milk. However no effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breastfeeding woman in negligible. Yellox can therefore be used during breastfeeding.

### 2.3.7. Conclusion on the non-clinical aspects

In general, the non-clinical properties of bromfenac have been adequately documented and meet the requirements to support this application.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

#### *GCP*

The Clinical trials were performed in accordance with GCP as claimed by the applicant. However, please see section 3.5.3.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| Type of Study | Study Identifier | Objective(s) of Study | Study Design and Type of Control | No. Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment |
|---|---|---|---|---|---|---|
| Pharmaco-kinetics | Senju F-27 | Pharmaco-kinetics | Phase I, open-label | 6 | Healthy subjects | Single dose |
| Pharmaco-kinetics | Senju G-01 | Pharmaco-kinetics, safety, tolerability | Phase I, open-label | 14<br>7 in each group | Healthy subjects | 28 days |
| Pivotal Phase III, Efficacy and safety | ISTA-BR-CS001-WR | Efficacy and safety | Phase III, multicentre, randomised, double-masked, placebo-controlled study. | 231<br>158 bromfenac<br>73 placebo | Patients ≥18 years old after unilateral cataract surgery with summed ocular inflammation score ≥3. | 14 days |
| Pivotal Phase III, Efficacy and safety | ISTA-BR-CS001-ER | Efficacy and safety | Phase III, multicentre, randomised, double-masked, placebo-controlled study. | 296<br>198 bromfenac<br>98 placebo | Patients ≥18 years old after unilateral cataract surgery with summed ocular inflammation score ≥3. | 14 days |
| Efficacy and safety | Senju G-05 | Efficacy and safety | Phase III randomised, double-masked, reference-therapy controlled. | 232<br>116 bromfenac<br>116 pranoprofen | Patients >15 years old with ocular inflammation after intraocular lens implant. | 14 days |
| Efficacy and safety | Senju G-02 | Efficacy and safety | Phase II, randomised, double-masked, reference-therapy controlled. | 160<br>87 bromfenac<br>73 pranoprofen | Patients ≥18 years with inflammation after cataract surgery or with anterior uveitis. | 14 days |
| Efficacy and safety | Senju G-06 | Efficacy and safety | Phase III, randomised, double-masked, reference-therapy controlled. | 222<br>111 bromfenac<br>111 pranoprofen | Patients ≥18 years with inflammation of external segment of eye, e.g., blepharitis, conjunctivitis | 14 days |
| Safety and tolerability | Croma Pharma 0503-ct/1 | Phase I, safety, tolerability | Phase I, randomised, double-blind active-comparator controlled. | 40<br>20 in each group | Healthy subjects | 14 days |
| Dose frequency response | Senju G-03 | Efficacy, safety and frequency of dose | Phase II, randomised, double-masked, multicentre. | 116<br>58 in each group | Patients ≥18 years after intraocular lens implant with ocular inflammation | 14 days |
| Dose concentration response | Senju G-04 | Efficacy, safety and dose concentration | Phase II, randomised, double-masked, multicentre. | 226<br>76: 0.01%<br>75: 0.1%<br>75: 0.2% | Patients ≥18 years after intraocular lens implant with ocular inflammation | 14 days |
| Efficacy and safety | Senju G-08 / -09 G-support. 01 / -02 | Efficacy and safety | Phase II, open-label | 96 | Patients ≥15 years old, who were scheduled to undergo intraocular lens implant. | Single dose |
| Efficacy and safety | Senju G-07 | Efficacy and safety | Phase III, open-label | 29 | Patients ≥18 years with inflammation of external segment of eye, e.g., blepharitis, conjunctivitis | 2 weeks |
| Efficacy and safety | Senju G-10 G-support. -03 | Efficacy and safety | Phase III, open-label | 51 | Patients ≥6 years of age with anterior uveitis with a flare of 15 to 200 photon counts/msec. | 2 to 14 weeks |

## 2.4.2. Pharmacokinetics

No ocular or systemic PK studies have been conducted with Yellox. However, two PK studies were conducted with the BFSS-OS formulation.

Study G-01 was a study in 14 healthy Japanese volunteers designed to assess the safety and blood concentrations of 0.1% (n=7) and 0.2% (n=7) BFSS-OS instilled in the eyes twice daily for 28 days. Samples were taken pre-dose and at 0.25, 0.5, 1 and 2 hrs post-dose day 1; 4hr post dose day 14 and 16hr post dose day 28 and 7 days post-study. No detectable plasma concentration was found in any subject.

Study F-27 was a study in healthy Japanese to characterize the metabolic disposition of a single dose of 14C-bromfenac (as the sodium salt) following oral administration. This study included 6 healthy volunteers. Excretion data were discharged for two of these due to mishandling.

### *Absorption*

In the Phase I healthy volunteer study G-01 the systemic concentration of bromfenac was below the limit of quantification (<50 ng/ml). The findings were consistent with the theoretical maximal systemic availability of bromfenac after ophthalmic instillation. Aqueous humour data were collected in a phase-II confirmatory study in 54 subjects undergoing cataract surgery (Miyake et al, 2008). Peak aqueous humour concentrations occurred between 150 and 180 min following 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*

Based on data following i.v. administration of bromfenac (Gumbhir-Shah et al, 1997), the volume distribution was approximately 0.15 L/kg. The in vitro plasma protein binding of 14C-bromfenac was assessed by equilibrium dialysis. At a bromfenac concentration of 1.4 µg/ml, the percent unbound was 0.16 in human plasma. A similar extent of binding was seen at a drug concentration of 10 µg/ml. At 53 µg/ml, however, the percent unbound increased from 0.16 to 0.21.

Bromfenac showed 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.

### *Elimination*

Based on data obtained following oral administration, the elimination pathways have been identified as metabolism followed by renal excretion of metabolites. Renal excretion of unchanged bromfenac only accounts for a very small part of the elimination. After ocular administration parent compound and/or metabolites were below measurable concentrations in the systemic circulation.

Based on literature data (i.v and oral), approximate values of bromfenac CLtot, CLr and t½ were 100 ml/min, 0.15 ml/min and 1.5 h, respectively.

In study F-27, the mean recovery of radioactivity in urine was 82.4%; and the mean recovery of radioactivity in faeces was 13.2%. The overall mean recovery of radioactivity was 95.6%. No free or conjugated bromfenac was detected in urine. Excretion into urine was rapid with most of the urinary radioactivity (66.5%) excreted during the first 8 hours.

### *Metabolism*

In-vivo

In study F-27, it was seen that except for an unidentified minor metabolite, unchanged bromfenac was the major component in plasma. The elimination rate of this minor metabolite appeared similar to bromfenac. Excretion into urine was rapid with most of the urinary radioactivity (66.5%) excreted during the first 8 hours. Profiles of the urinary metabolites changed over time. In the urine up to 4 hours post-dose, cyclic amide (AHR-10240) was the major metabolite. In the urine 4 to 12 hours post-dose, the AHR-10240 peak decreased in size and four polar peaks predominated. These peaks appeared to be glucuronide conjugates of unidentified aglycones. A total of 13.2% of the dose was recovered in faeces. No characterisation of the faecal radioactivity was performed. The overall mean recovery of radioactivity in the study was 95.6%.

In-vitro

One in vitro study with the aim of identifying P450 enzymes involved in metabolism of bromfenac was performed. Thin layer Chromatography (TLC) was selected as the appropriate method to identify human P450 enzymes (1A2, 2C9, 2D6, 2E1, CYP2C9, 3A4) involved in metabolism of bromfenac sodium. Bromfenac sodium was 14C labelled. The experiments were performed in human P450-expressing microsomes and in human liver microsomes. Results suggest that a single P450 enzyme, CYP2C9*1 (Arg), is responsible for bromfenac's metabolism.

### *Special populations*

The PK of bromfenac following ocular administration has not been investigated in any special populations.

Following oral administration, no marked effects of gender, age and renal disease on bromfenac´s PK was seen. Hepatic impairment led to a change in bromfenac´s PK where patients with mild to moderate cirrhosis had a 40 % lower clearance as compared with healthy volunteers. The potential impact of race and weight has not been reported.

### *Pharmacokinetic interaction studies*

No formal PK interaction studies have been conducted with BFSS-OS. In the Phase III studies, most patients received topical or intracameral antibiotics to minimize the risk of post-operative endophthalmitis, which is a rare complication of cataract surgery.

## 2.4.3. Pharmacodynamics

No specific pharmacodynamic studies in humans have been performed. Available data come from pre-clinical studies and have been discussed in the corresponding section.

No specific pharmacodynamic interaction studies have been performed. This was considered acceptable. However, if more than one topical ophthalmic medicinal product is being used, an appropriate time of at least 5 minutes between the two administrations is recommended. This is reflected in section 4.2 of the SmPC.

## 2.4.4. Discussion on clinical pharmacology

No PK studies have been performed with Yellox and only limited data exist from studies performed with the formulation approved in US and Japan.

The most important PK study was the phase I healthy volunteer study G-01 where it was shown that the systemic exposure of bromfenac following ocular administration was very low compared to what is observed following oral administration.

A rough estimation of a worst case systemic exposure to bromfenac following ocular administration gave a theoretical maximum plasma concentration of approximately 20 ng/ml (52 nM).

While it is accepted from extrapolation that systemic exposure is likely to be low, the IC50 with respect to COX-2 and COX-1 inhibition is about 7 and 210 nM, respectively. It is, however, very reassuring that the currently sought formulation has been used in clinical practice with only very rare reports of suspected systemic adverse reactions.

Metabolism was studied in human P450- expressing microsomes (1A2, 2C9, 2D6, 2E1, CYP2C9, 3A4) and in human liver microsomes. Results suggested that a single P450 enzyme, CYP2C9, catalyzed the metabolism of bromfenac.

Clinically relevant drug-drug interactions were not considered to be an issue as systemic exposure, while undefined, was below 130 nM.

## 2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of bromfenac is of limited relevance in this application as the plasma levels are below limit of quantification following ocular administration. The only part contributing to the benefit/risk assessment was from a safety perspective where the pharmacokinetic data described the low systemic exposure following ocular administration as compared to oral administration.

Given the low systemic exposure of bromfenac, the risk for systemic PK interactions and potential differences in certain special populations (gender, age, renal impairment, hepatic impairment etc.) from a PK point of view was considered to be low.

# *2.5. Clinical efficacy*

## 2.5.1. Dose response studies

The phase II studies encompassed 2 studies conducted in Japan: G-03, where a twice daily regimen was compared to a 4 times daily regimen, and G-04 in which 3 different concentrations of bromfenac (0.1 %, 0.2 %, and 0.01 %) ophthalmic solution were compared.

**Study G-04**

The study aim was to determine the efficacy, safety and optimum concentration of the ophthalmic bromfenac solution of the 3 concentrations 0.2 %, 0.1 %, and 0.01 % in patients with anterior uveitis following intraocular lens transplantation.

The study population encompassed patients who had undergone intraocular lens implant, had anterior uveitis (inflammation) and had received preoperative ophthalmic indomethacin solution were eligible for study enrolment. The main exclusion criteria were a flare value on postoperative day 1 of ≤20 or ≥400 photon counts/msec. The planned sample size was 300 patients, 100 patients in each group.

Patients were randomised to receive BFSS-OS 0.2%, 0.1% or 0.01%. One drop of test agent was administered twice daily (morning and evening). The planned treatment duration was 2 weeks.

Assessments were performed preoperatively and on postoperative days 1 (prior to study drug administration), 3, 8 and 15. Investigators made a global assessment of efficacy based on the degree of improvement in anterior chamber protein (ACP) and overall clinical findings with the following guidelines: markedly effective (+/- to – in ACP); effective (improvement in ACP by one or more levels); ineffective (no changed in ACP); deteriorated (worsening in ACP by one or more levels).

The patient disposition is shown in the table below.

**Table 1: Patient Disposition, No. Patients – Senju Study G-04**

| | **BFSS-OS** | | |
|---|---|---|---|
| | **0.01%** | **0.1%** | **0.2%** |
| **Enrolled** | 77 | 75 | 76 |
| **Safety Population** | 76 | 75 | 75 |
| **Investigator Evaluable Population** | 72 | 71 | 69 |

BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution

The evaluation of efficacy is summarised in the table below.

**Table 2: Evaluation of efficacy by investigators, No Patients (%) – Senju Study G-04.**

| | | **BFSS-OS** | | |
|---|---|---|---|---|
| | | **0.01%, N=72** | **0.1%, N=71** | **0.2%, N=69** |
| Effective or markedly effective | | 46 (63.9) | 64 (90.1) | 59 (85.5) |
| Markedly effective | | 11 (15.3) | 18 (25.3) | 16 (23.2) |
| Effective | | 35 (48.6) | 46 (64.8) | 43 (62.3) |
| Ineffective | | 20 (27.8) | 4 (5.6) | 8 (11.6) |
| Deteriorated | | 6 (8.3) | 3 (4.2) | 2 (2.9) |
| Kruskal-Wallis [H] test | 0.01% vs 0.1% vs 0.2% | $\chi^2_0$=12.3106 (df=2); $P_0$=0.0021 | | |
| | 0.2% vs 0.1% | $Z_0$=0.6081; $P_0$=0.5431 | | |
| | 0.2% vs 0.01% | $Z_0$=2.6691; $P_0$=0.0076 | | |
| | 0.1% vs 0.01% | $Z_0$=3.2176; $P_0$=0.0013 | | |

Patient base: Investigator Evaluable Population

BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; df: degrees of freedom; vs: versus

The conduct of the study raised numerous major problems. In this respect, the extension of the duration of treatment to more than 15 days (2 weeks were planned) for a considerable part of patients, namely 48/112, was remarkable – particularly as the observation point for the efficacy results was unknown. In addition, the maximal duration of treatment was stated to be ≥ 50 days in 2 of the 3 treatment groups. Exact time point of observation for these results was not provided. The treatment period was stipulated to be 2 weeks. No observation after Day 8 has been given in the study report.

The planned sample size of 300 was not reached as only 212 subjects were included in the study. Moreover, 44 patients received concurrent medication, which is not specified in a way to detect ocular medication, which might influence the outcome.

With due reservations, a comparable effect of the 0.1 % and the 0.2 % bromfenac concentrations in the ophthalmic solutions was considered likely.

Based on this study, no firm conclusions could be drawn on the efficacy, safety and optimum concentration of the ophthalmic bromfenac solution of the 3 concentrations 0.2 %, 0.1 %, and 0.01 %.

**Study G-03**

The study aim was to evaluate the efficacy and safety of bromfenac eye drops in two different dosing regimens: Twice daily or 4 times daily administration in patients with inflammation following cataract surgery.

Patients who had undergone intraocular lens implant and had received preoperative ophthalmic indomethacin solution were eligible for study enrolment. The main exclusion criteria were a flare value on postoperative day 1 of ≤20 photon counts/msec.

A single drop of BFSS-OS 0.1% was instilled by the subject into the study eye twice daily (morning and night) or 4 times daily (morning, noon, evening, and night) starting approximately 24 hours after cataract surgery and continuing for up to 14 days.

Overall degree of improvement based on the findings in the anterior chamber determined by laser flare meter and by overall clinical findings. The Investigator graded as follows: Markedly improved, Improved, Slightly improved, Unchanged, or Worse.

**Table 3: Patient disposition, No.patients – Senju Study G-03**

| | **BFSS-OS 0.1%** | |
|---|---|---|
| | **Twice Daily** | **4-times Daily** |
| **Enrolled** | 58 | 58 |
| **Safety Population** | 58 | 58 |
| **Prohibited Medication** | 1 | 6 |
| **Secondary implant of anterior chamber lens** | 1 | 0 |
| **Only one dose of test agent** | 2 | 1 |
| **Investigator Evaluable Population** | 54 | 51 |

BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution

The results obtained for the main parameters are shown in the table below.

**Table 4: Evaluation of efficacy by investigators, No Patients (%) – Senju Study G-03.**

| | **BFSS-OS 0.1%** | |
|---|---|---|
| | **Twice Daily, N=54** | **4-times Daily, N=51** |
| **Improved or markedly improved** | 32 (59.3) | 30 (58.8) |
| **Markedly improved** | 7 (13.0) | 5 (9.8) |
| **Improved** | 25 (46.2) | 25 (49.0) |
| **Slightly improved** | 20 (37.0) | 20 (39.2) |
| **Unchanged** | 2 (0.4) | 0 |
| **Deteriorated** | 0 | 1 (0.2) |
| **Kruskal-Wallis (H) test** | $Z_0$=0.1543; $P_0$=0.8773 | |

Patient base: Investigator Evaluable Population

BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution

The Applicant stated that the rate of patients improvement and marked improvement was similar for BFSS-OS b.i.d (59.3%, 32/54) and BFSS-OS q.i.d. (58.8%, 30/51), with no significant difference between groups ($Z_0$=0.1543; $P_0$=0.8773, Kruskal-Wallis [H] test).

Based on the obtained figures, it appeared to be no differences in efficacy when comparing BID with QID administration of 0.1 % BFSS-OS. However, no clear conclusions could be drawn based on this trial as the conduct of the study raised numerous major problems.

The planned sample size of 150 was far from being reached with the number of 105 subjects available for efficacy analysis. Furthermore, the study was not double-masked as no "double-dummy" technique was employed. In addition, the time for the observed results was not stated and the extension of the duration of treatment to more than 15 days and the maximum treatment duration of 29 days were also an unexplained matter. Finally, some patients received concurrent medication, which was not specified in a way to catch ocular medication.

In conclusion, the optimal dosing regimen has not been unequivocally determined.

For both phase II studies G-04 and G-03, although the proposed concentration and dosing frequency (0.1 % BFSS-OS, BID) did not appear unreasonable, overall, the value of the 2 trials to determine the optimal dosing regimen and the optimal drug concentration was considered limited because of grave methodological and procedural shortcomings.

## 2.5.2. Main studies

**ISTA-BR-CS001-ER and ISTA-BR-CS001-WR**

### *Methods*

Two pivotal trials, ISTA-BR-CS001-ER and ISTA-BR-CS001-WR were conducted following the same protocol. They were randomised multi-centre double masked parallel study investigating the efficacy and safety of topical Bromfenac ophthalmic solution 0.1 % versus placebo for treatment of ocular Inflammation following cataract surgery. They were both conducted in the USA.

- ***Study Participants***

Patients were male or female subject of at least 18 years of age scheduled for unilateral cataract surgery (phacoemulsification or extracapsular extraction) with posterior chamber intraocular lens implantation. A summed score of ≥ 3 for anterior chamber cells (scale 0-4) and flare (scale 0-4) at the baseline examination (visit 1, study day 1) was required. No concurrent use of anti-inflammatory drugs, topical or systemic, during the study (treatment and follow-up stages) was allowed.

- ***Treatments***

Each subject self-instilled a one-drop dose of test agent, either bromfenac 0.1% or placebo control, twice daily, beginning 16 to 32 hours after surgery and continuing for duration of 14 days (total of 28 doses).

The therapy was scheduled for up to 14 days with study visits at Day 3, Day 8, Day 15, Day 22, Day 29, and at early discontinuation of the study.

- ***Objectives***

The primary objective of those two studies was to investigate the efficacy of bromfenac sodium ophthalmic solution 0.1 % for the treatment of post-operative ocular inflammation in subjects undergoing cataract extraction with posterior intraocular chamber lens implantation. The secondary aim was to investigate the safety and tolerability of the eye drops in this condition.

- ***Outcomes/endpoints***

The primary endpoint was the proportion of patients in the ITT group with cleared ocular inflammation in the study eye at visit 4 (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.

A number of 16 secondary endpoints were used. The most relevant/pertinent secondary endpoints were time to resolution of pain and time to resolution of ocular inflammation, and the proportion of patients who used rescue medication.

The definitions of determination of the grading of the ocular inflammation parameters are shown in the table below.

**Table 5: Anterior chamber cell counts and flare grade for determining the summed ocular inflammation score patients**

| **Anterior Chamber Cells** | | **Anterior Chamber Flare** | |
|---|---|---|---|
| 0 | None-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 |

The summed Ocular Inflammation Score (SOIS) was obtained by adding the anterior chamber cell and flare scores. The minimum SOIS was zero and the maximum was 8.
For evaluation, a slit-lamp biomicroscopy was used at a ×16 magnification with a 1×1-mm oblique high-intensity beam.

- ***Sample size***

Assuming that 60% of the bromfenac-treated patient and 35% of the vehicle-treated patient would have cleared the ocular inflammation (a sum inflammation score of zero) at Day 15 a sample size of 202 patients (135 bromfenac and 67 placebo) and a two-sided α of 0.049 and a power of 0.90 % was necessary. Allowing safety data for at least 300 patients in the two protocols a total of 450 patients were needed in the two trials corresponding to 225 in each study.

- ***Randomisation***

Subjects were sequentially assigned, according to a computer-generated randomisation list, to one of two treatment groups in a 2:1 ratio to receive either bromfenac ophthalmic solution 0.1% or placebo. Within each centre, subjects were randomised using a blocked randomisation scheme with a block size of six.

- ***Blinding (masking)***

The Applicant claimed that those two studies were double-blind studies. However the GCP inspection that was performed revealed that the active and the placebo of the Investigational Medicinal Product (IMP) were different in appearance. The active IMP was yellow and the placebo was colourless. The yellow appearance of the active drug also gave a yellow appearance to the bottles. The IMP did therefore not qualify as double-blinded.

In addition, blinded staffs such as nurses or study coordinators handled the IMP, opened the boxes, pealed of the seal from the immediate containers of the blinded IMP and were present immediately

next to the trial subjects during administration of the blinded IMP. The nurses or study coordinators also handled the labels from both bottles and boxes.

- ***Statistical methods***

The primary analysis employed the proportion of subjects who achieved cleared ocular inflammation at the Day 15 visit. Differences were examined with either chi square or Fisher's exact test.

- **Recruitment**

In ISTA-BR-CS001-ER 20 centres east of Mississippi and in ISTA-BR-CS001-WR 19 centres west of Mississippi recruited patients.

In both trials the first patient was randomised in May 2003 and the last visit was terminated in January 2004.

- **Conduct of the study**

A long list of protocol amendments was issued; however, no participants were enrolled prior to the changes.

## *Results*

- **Participant flow**

The disposition of patients in studies ISTA-BR-CS001-WR and ISTA-BR-CS001-ER, respectively, is shown in the tables below.

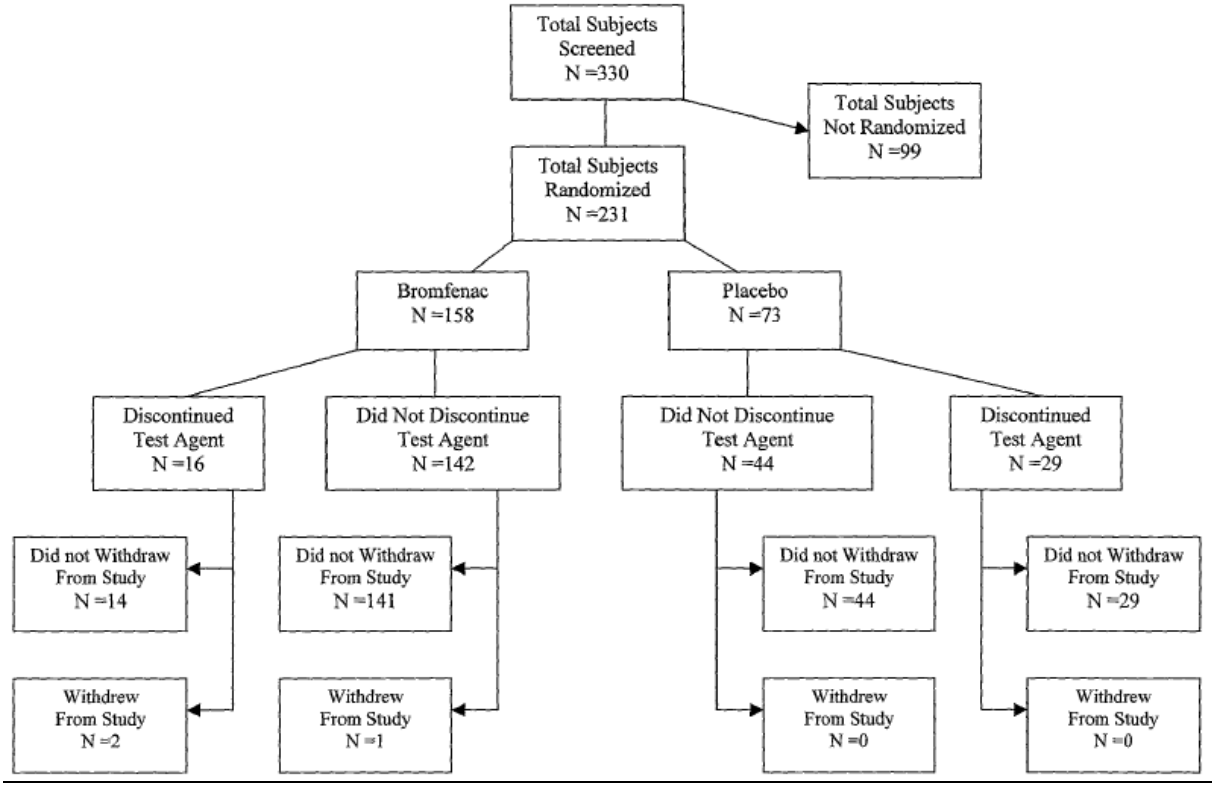
### STUDY ISTA-BR-CS001-WR

**Table 6: Disposition for randomised patients, No. Patients (%) – Study ISTA-BR-CS001-WR**

| | **BFSS-OS 0.1%** | **Placebo** | **P value** [a)] |
|---|---|---|---|
| **N** | 158 | 73 | --- |
| **Completed study** | 155 (98.1) [b)] | 73 (100) | --- |
| **Discontinued treatment** | 16 (10.1) | 29 (39.7) | <0.0001 |
| **Lack of tolerability of test agent** | 1 (0.6) | 0 | NS |
| **Adverse event** | 4 (2.5) | 11 (15.1) | 0.0007 |
| **Disallowed concurrent medication** | 3 (1.9) | 1 (1.4) | NS |
| **Lack of efficacy** | 5 (3.2) | 16 (21.9) | <0.0001 |
| **Other reason** | 3 (1.9) | 1 (1.4) | NS |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
a) Based on Chi-square or Fisher's exact test.
b) Reasons for premature study discontinuation for the three patients in the bromfenac group were withdrawal of consent/compliance; hospitalisation for severe stroke; and accidental randomisation of an ineligible subject.
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; NS: not significant

FIGURE 1: SUBJECT DISPOSITION – ISTA-BR-CS001-WR



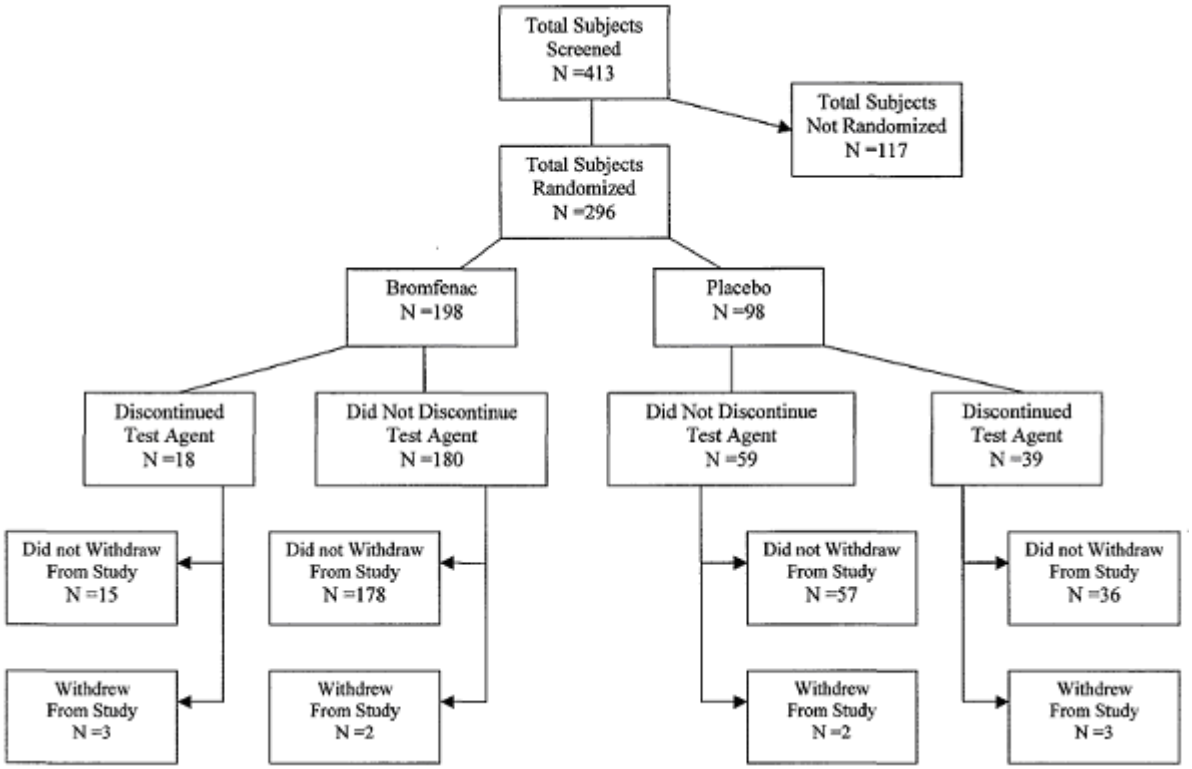

**STUDY ISTA-BR-CS001-ER**

**Table 7: Disposition for randomised patients, No. Patients (%) – Study ISTA-BR-CS001-ER**

| | **BFSS-OS 0.1%** | **Placebo** | **P value [a)]** |
|---|---|---|---|
| **N** | 198 | 98 | |
| **Completed study** | 193 (97.4) | 93 (94.9) | |
| **Discontinued study** | 5 (2.5) | 5 (5.1) | NS |
| **Withdrawal of consent/non-compliance** | 2 (1.0) | 2 (2.0) | NS |
| **Loss to follow-up** | 1 (0.5) | 1 (1.0) | NS |
| **Other reason [b)]** | 2 (1.0) | 2 (2.0) | NS |
| **Discontinued treatment** | 18 (9.1) | 39 (39.8) | <0.0001 |
| **Lack of tolerability of test agent** | 0 | 1 (1.0) | NS |
| **Adverse event** | 6 (3.0) | 14 (14.3) | 0.0003 |
| **Disallowed concurrent medication** | 2 (1.0) | 2 (2.0) | NS |
| **Lack of efficacy** | 6 (3.0) | 21 (21.4) | <0.0001 |
| **Other reason [c)]** | 4 (2.0) | 1 (1.0) | NS |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; NS: not significant.
a) Based on chi-square or Fisher's exact test.
b) "Other" reasons for premature study discontinuation were 1 patient with prolonged hospitalisation in the bromfenac group (narrative in Section 14.3 of report) and 1 patient who had been accidentally enrolled in the placebo group (insufficient baseline ocular inflammation score).
c) "Other" reasons for premature treatment discontinuation were lack of patient compliance (3 patients) and accidental enrolment (baseline flare <3) in the BFSS-OS group; and 1 patient with lack of compliance in the placebo group.

FIGURE 2: SUBJECT DISPOSITION – ISTA-BR-CS001-ER




- **Baseline data**

The demographic distribution of patients in studies ISTA-BR-CS001-WR and ISTA-BR-CS001-ER, respectively, is depicted below.

**Table 8: Patient Demographics and Baseline Characteristics (Pre-surgery screening Visit), No.Patients (%) – Study ISTA-BR-CS001-WR**

| | | BFSS-OS 0.1% | Placebo | Total | P value |
|---|---|---|---|---|---|
| N | | 158 | 73 | 231 | |
| Age | Mean ± SD | 70.3 ± 9.4 | 68.8 ± 11.4 | 69.9 ± 10.0 | 0.3183 [a] |
| | Median | 72.0 | 69.0 | 72.0 | |
| | Min-Max | 42.0 – 93-0 | 32.0 – 91.0 | 32.0 – 93.0 | |
| Gender, No. (%) | Male | 69 (43.7) | 42 (57.5) | 111 (48.1) | 0.0499 [b] |
| | Female | 89 (56.3) | 31 (42.5) | 120 (51.9) | |
| Race, No. (%) | Caucasian | 134 (84.8) | 64 (87.7) | 198 (85.7) | 0.8824 [b] |
| | Hispanic | 14 (8.9) | 4 (5.5) | 18 (7.8) | |
| | Black | 5 (3.2) | 3 (4.1) | 8 (3.5) | |
| | Other | 5 (3.2) | 2 (2.7) | 7 (3.0) | |
| Study Eye | | | | | |
| Iris colour, No. (%) | Brown | 69 (43.7) | 27 (37.0) | 96 (41.6) | 0.0284 [b] |
| | Blue | 57 (36.1) | 20 (27.4) | 77 (33.3) | |
| | Hazel | 17 (10.8) | 17 (23.3) | 34 (14.7) | |
| | Green | 8 (5.1) | 8 (11.0) | 16 (6.9) | |
| | Other | 7 (4.4) | 1 (1.4) | 8 (3.5) | |
| Summed Ocular Inflammation Score | Min | 0.0 | 0.0 | 0.0 | 1.0000 [c] |
| | Max | 0.0 | 0.0 | 0.0 | |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
P-value for bromfenac versus placebo based on: a) T test; b) chi-square or Fisher's exact test; c) Wilcoxon rank sum test
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution

**Table 9: Patient Demographics and Baseline Characteristics (Pre-surgery screening Visit), No.Patients (%) – Study ISTA-BR-CS001-ER**

| | | BFSS-OS 0.1% | Placebo | Total | P value |
|---|---|---|---|---|---|
| N | | 198 | 98 | 296 | |
| Age | Mean ± SD | 69.3 ± 10.1 | 70.4 ± 9.2 | 69.7 ± 9.8 | 0.3429 [a] |
| | Median | 71.0 | 71.0 | 71.0 | |
| | Min-Max | 35.0, 88.0 | 40.0, 93.0 | 35.0, 93.0 | |
| Gender, No. (%) | Male | 93 (47.0) | 42 (42.9) | 135 (45.6) | 0.5038 [b] |
| | Female | 105 (53.0) | 56 (57.1) | 161 (54.4) | |
| Race, No. (%) | Caucasian | 162 (81.8) | 73 (74.5) | 235 (79.4) | 0.5304 [b] |
| | Hispanic | 11 (5.6) | 9 (9.2) | 20 (6.8) | |
| | Black | 20 (10.1) | 14 (14.3) | 34 (11.5) | |
| | Other | 5 (2.5) | 2 (2.0) | 7 (2.4) | |
| Study Eye | | | | | |
| Iris colour, No. (%) | Brown | 85 (42.9) | 45 (45.9) | 130 (43.9) | 0.6662 [b] |
| | Blue | 58 (29.3) | 32 (32.7) | 90 (30.4) | |
| | Hazel | 33 (16.7) | 10 (10.2) | 43 (14.5) | |
| | Green | 19 (9.6) | 9 (9.2) | 28 (9.5) | |
| | Other | 3 (1.5) | 2 (2.0) | 5 (1.7) | |
| Summed Ocular Inflammation Score | Min | 0.0 | 0.0 | 0.0 | 1.0000 [c] |
| | Max | 0.0 | 0.0 | 0.0 | |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
P-value for bromfenac versus placebo based on: a) T test; b) chi-square of Fisher's exact test; c) Wilcoxon rank sum test
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution

## Numbers analysed

**Table 10: ITT, ITT censored, and PP populations in Studies ISTA-BR-CS001-ER and ISTA-BR-CS001-WR**

| | | BFSS-OS 0.1% | Placebo |
|---|---|---|---|
| **ITT, LOCF[a)]** | **Study ISTA-BR-CS001-ER** | 198 | 98 |
| | **Study ISTA-BR-CS001-WR** | 158 | 73 |
| **ITT, LOCF Censored [b)]** | **Study ISTA-BR-CS001-ER** | 198 | 98 |
| | **Study ISTA-BR-CS001-WR** | 158 | 73 |
| **Per protocol [c)]** | **Study ISTA-BR-CS001-ER** | 117 | 33 |
| | **Study ISTA-BR-CS001-WR** | 90 | 33 |

BFSS-OS: bromfenac sodium sesquihydrate, ophthalmic solution; ITT: Intent-to-treat Population (all patients randomised to test agent); LOCF: last observation carried forward.

a) Primary analysis, not censored; represents not only the test agent but also the rescue medication at study day 15.

b) Data for patients who discontinued test agent and received rescue medication were counted as treatment failures.[3]

c) Patients had no disallowed medications, met eligibility criteria, had a Visit 4 on study day 14-16 and other study visits according to the statistical analysis plan and had at least 22 doses of test agent.

## Outcomes and estimation

### Primary efficacy parameters

Results of the primary efficacy parameters for the ITT (last observation carried forward, LOCF) are depicted in the tables below.

For patients who prematurely discontinued test agent and were provided with an alterative anti-inflammatory medication, this analysis represents not only the test agent but also the rescue medication at Study Day 15.

#### STUDY ISTA-BR-CS001-WR

**Table 11: Primary Efficacy Analysis: Summed Ocular Inflammation Score Equal to Zero on Visit 4 (Day 15), LOCF, No. Patients (%) – Study ISTA-BR-CS001-WR**

| | BFSS-OS 0.1% | Placebo | P value |
|---|---|---|---|
| **N** | 158 | 73 | |
| **Primary analysis, LOCF (no censoring) [a)]** | 104 (65.8) | 35 (47.9) | 0.0099 [b)] |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; LOCF: last observation carried forward.
a) For patients who prematurely discontinued test agent and were provided with an alterative anti-inflammatory medication, this analysis represents not only the test agent but also the rescue medication at Visit 4.
b) chi-square test

[3] Text according to study report: Data for patients who discontinued test agent were censored at the visit closest to (on or before) the receipt of the alternative medication for inflammation (that is, analysis represents the percentage of subjects who cleared while only receiving test agent treatment).

The primary analysis (ITT, LOCF) showed a statistically significant higher proportion of patients in the BFSS-OS group (65.8%, 104/158) than in the placebo group (47.9%, 35/73) to have experienced clearance of ocular inflammation of Visit 4 (Day 15, EOT) (P=0.0099).

**STUDY ISTA-BR-CS001-ER**

**Table 12: Primary Efficacy Analysis: Summed Ocular Inflammation Score Equal to Zero on Visit 4 (Day 15), LOCF, No. Patients (%) – Study ISTA-BR-CS001-ER**

| | BFSS-OS 0.1% | Placebo | P value |
|---|---|---|---|
| **N** | 198 | 98 | |
| **Primary analysis, LOCF (no censoring) a)** | 124 (62.6) | 39 (39.8) | 0.0002 b) |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; LOCF: last observation carried forward.
a) For patients who prematurely discontinued test agent and were provided with an alterative anti-inflammatory medication, this analysis represents not only the test agent but also the rescue medication at Visit 4.
b) chi-square test

The primary analysis (ITT, LOCF) showed a statistically significant higher proportion of patients in the BFSS-OS group (62.6%, 124/198) than in the placebo group (39.8%, 39/98) to have experienced clearance of ocular inflammation at Visit 4 (Day 15, EOT) (P=0.0002, chi-square test). There was no significant site-by-treatment interaction (P=0.5339).

The tables below summarise an analysis of the ITT, in which data from patients were censored at the time of discontinuation of test agent (receipt of an alternative anti-inflammatory medicine).

**STUDY ISTA-BR-CS001-WR**

In the absence of other anti-inflammatory medications in the ITT population (censoring of data at the time receipt of an alternative anti-inflammatory medicine in both treatment groups), the rate of clearance of ocular inflammation was higher for the BFSS-OS group (62.0%, 98/158) than the placebo group (31.5%, 23/73), and the difference was statistically significant (P<0.0001).

**Table 13: Summed Ocular Inflammation Score Equal to Zero on Visit 4 (Day 15), LOCF, Censored, No. Patients (%) – Study ISTA-BR-CS001-WR**

| | BFSS-OS 0.1% | Placebo | P value |
|---|---|---|---|
| **N** | 158 | 73 | |
| **With test agent only a)** | 98 (62.0) | 23 (31.5) | <0.0001 b) |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
a) Patient data were censored at the visit closest to (on or before) the receipt of the alternative medication for inflammation (that is, analysis represents the percentage of subjects who cleared while only receiving test agent treatment). b) chi-square test or Fisher's exact test
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; LOCF: Last observation carried forward.
Source: ISTA-BR-CS001-WR Study Report, Section 14.2, Table 18

**STUDY ISTA-BR-CS001-ER**

In the absence of other anti-inflammatory medications in the ITT population *(censoring of data at the time receipt of an alternative anti-inflammatory medicine in both treatment groups*), the rate of clearance of ocular inflammation was higher for the BFSS-OS group (57.1%, 113/198) than the placebo group (23.5%, 23/98), and the difference was statistically significant (P<0.0001, chi-square or Fisher's exact test).

**Table 14: Summed Ocular Inflammation Score Equal to Zero on Visit 4 (Day 15), LOCF, Censored, No. Patients (%) – Study ISTA-BR-CS001-ER**

| | BFSS-OS 0.1% | Placebo | P value |
|---|---|---|---|
| **N** | 198 | 98 | |
| **With test agent only** [a)] | 113 (57.1) | 23 (23.5) | <0.0001 [b)] |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
a) Patient data were censored at the visit closest to (on or before) the receipt of the alternative medication for inflammation (that is, analysis represents the percentage of subjects who cleared while only receiving test agent treatment).
b) chi-square test or Fisher's exact test
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; LOCF: last observation carried forward.

In both trials, the signs of ocular inflammation disappeared faster in the bromfenac group than in the vehicle group, as shown in the tables below.

**Table 15: Ocular Inflammation Score of Zero by Study Visit, LOCF, Censored, No. Patients (%) – Study ISTA-BR-CS001-WR**

| | N | Visit 2 Day 3 | Visit 3 Day 8 | Visit 4 Day 14, EOT | Visit 5 Day 22 | Visit 6 Day 29 |
|---|---|---|---|---|---|---|
| **BFSS-OS** | 158 | 17 (10.8) | 60 (38.0) | 98 (62.0) | 106 (67.1) | 126 (79.7) |
| **Placebo** | 73 | 1 (1.4) | 11 (15.1) | 23 (31.5) | 27 (37.0) | 38 (52.1) |
| **P value** [a)] | | 0.0133 | 0.0005 | <0.0001 | <0.0001 | <0.0001 |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
Patients who received a rescue medication were censored at the time of receipt of the medication
a) chi-square or Fisher's exact test
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; EOT: end of therapy; LOCF: Last observation carried forward

**Table 16: Ocular Inflammation Score of Zero by Study Visit, LOCF, Censored, No. Patients (%) – Study ISTA-BR-CS001-ER**

| | N | Visit 2 Day 3 | Visit 3 Day 8 | Visit 4 Day 14, EOT | Visit 5 Day 22 | Visit 6 Day 29 |
|---|---|---|---|---|---|---|
| **BFSS-OS** | 198 | 13 (6.6) | 64 (32.3) | 113 (57.1) | 128 (64.6) | 159 (80.3) |
| **Placebo** | 98 | 1 (1.0) | 12 (12.2) | 23 (23.5) | 40 (40.8) | 47 (48.0) |
| **P value** [a)] | | 0.0403 | 0.0002 | <0.0001 | <0.0001 | <0.0001 |

Patient base: Intent-to-treat Population (all patients randomised to test agent).

Patients who received a rescue medication were censored at the time of receipt of the medication.

a) chi-square or Fisher's exact test

BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; EOT: end of therapy; LOCF: Last observation carried forward

**Secondary efficacy parameters**

In the two studies, the secondary efficacy findings were consistent with the results obtained for the primary efficacy parameters. Of particular interest were the median time to resolution of ocular pain and the proportion of patients whose discontinued the test agent due to lack of efficacy.

Time to resolution of ocular pain was defined as the number of days from baseline, visit 1, to the visit at which the score was 0 (none). Ocular pain was obtained from the subject diary and defined as none, mild, moderate or severe within one hour after instillation of the medication. Analysis included only subjects with ocular pain on study day 1. Subjects were right censored at receipt of rescue medication or at the last visit if the pain was not cleared.

In study ISTA-BR-CS001-WR, the median time to resolution of ocular pain was 2 days for the BFSS-OS group and 5.0 days for the placebo group (P<0.0001, log rank test, comparison of Kaplan-Meier curves) (ITT) and the proportion of patients who discontinued test agent due to lack of efficacy was significantly lower for patients in the BFSS-OS group (3.2%, 5/158) than in the placebo group (21.9%, 16/73) (P<0.0001, chi-square or Fisher's exact test).

In study ISTA-BR-CS001-ER, the median time to resolution of ocular pain was 2 days for the BFSS-OS group and 4 days for the placebo group (P<0.0001, log rank test, comparison of Kaplan-Meier curves) (ITT) and the proportion of patients who discontinued test agent due to lack of efficacy was significantly lower for patients in the BFSS-OS group (3.0%, 6/198) than in the placebo group (21.4%, 21/98) (P<0.0001, chi-square or Fisher's exact test).

## Ancillary analysis

A large window (16-32 hours) for the interval from surgery to the first dose of the test drug was allowed by the study protocol. During the review process, the Applicant was asked to discuss the possible differences in the outcome depending of how soon the therapy is initiated.

Nearly all patients started randomised treatment within this time window: 96.9% (344/355) of patients in the BFSS OS group and 98.2% (168/171) in the placebo group. This subset of patients (those who started treatment between 16 and 32 hours following cataract surgery) showed no difference in the rates of treatment success (SOIS=0 at Visit 4) for those who started treatment between 16 and 24 hours following surgery compared to those who started treatment >24 to 32 hours following surgery.

A second analysis was done for all patients, including the few patients who started randomized treatment outside the limits of 16 to 32 hours following cataract surgery. Whether treatment was initiated within 24 hours following surgery or afterwards had no effect on treatment outcome. In the

ITT LOCF BFSS-OS group, treatment success (SOIS=0 at Visit 4) was reported for 62.3% (114/183) of the patients who started randomized treatment within 24 hours following cataract surgery versus 65.7% (113/172) for patients who started randomized treatment after 24 hours (P=0.510, Fisher's exact test)). In the ITT LOCF placebo group, treatment success was reported for 46.4% (39/84) of the patients who started randomized treatment within 24 hours following cataract surgery versus 39.1% (34/87) for patients who started randomized treatment after 24 hours (P=0.357, Fisher's exact test).

It could be concluded from these analyses that most patients started randomized treatment within 16 to 32 hours following cataract surgery; and that treatment outcome was consistent regardless of whether treatment was started within 16 to 24 hours following surgery or >24 to 32 hours following surgery.

## Analysis performed across trials

The two pivotal trials conducted with the same protocol have been pooled, and results for the primary analysis are shown below:

**Table 17: Primary Efficacy Analysis: Summed Ocular Inflammation Score Equal to Zero on Visit 4 (Day 15), LOCF, No. Patients (%) – Studies ISTA-BR-CS001-ER and ISTA-BR-CS001-WR, Pooled Analysis**

| | **BFSS-OS 0.1%** | **Placebo** | **P value** |
|---|---|---|---|
| **N** | 356 | 171 | |
| **Primary analysis, ITT, LOCF (no censoring)** [a)] | 228 (64.0) | 74 (43.3) | <0.0001 [b)] |
| **N** | 356 | 171 | <0.0001 [b)] |
| **ITT, LOCF censored** [c)] | 211 (59.3) | 46 (26.9) | |
| **N** | 207 | 66 | |
| **PP population** | 139 (67.1) | 30 (45.5) | 0.0011 |

Patient base: Intent-to-treat Population (all patients randomised to test agent).
BFSS-OS: Bromfenac sodium sesquihydrate, ophthalmic solution; LOCF: last observation carried forward.
a) For patients who prematurely discontinued test agent and were provided with an alterative anti-inflammatory medication, this analysis represents not only the test agent but also the rescue medication at Study Day 15.
b) Cochran-Mantel-Haenszel procedure
c) Data for patients who discontinued test agent were censored at the visit closest to (on or before) the receipt of the alternative medication for inflammation (thus, patients who cleared while receiving rescue therapy were counted as treatment failures).

The primary analysis (ITT, LOCF) showed a statistically significant higher proportion of patients in the BFSS-OS group (64.0%, 228/356) than in the placebo group (43.3%, 74/171) to have experienced clearance of ocular inflammation at Visit 4 (Day 15, EOT) (P<0.0001, C-M-H). The result is supported by the secondary analysis in the PP population.

With censoring at the time of treatment discontinuation (receipt of rescue medication) in the ITT, 59.3% (211/356) of patients in the BFSS-OS group and 26.9% (46/171) of patients in the placebo group had clearance of ocular inflammation at Visit 4 (Day 15, EOT) (P<0.0001).

## Clinical studies in special populations

No studies have been performed in special populations

## Supportive studies

### STUDY G-05

This double masked study was conducted in Japan in 1993/1994. The aim was to compare bromfenac eye drops 0.1 % twice daily with pranoprofen eye drops 0.1% eye drops 4 times daily for 2 weeks in patients with anterior uveitis after cataract surgery. Since pranoprofen is approved in a number of EU countries it was considered to be a valid comparator. The primary endpoint was the Investigator's evaluation of the finding in patient's anterior chamber protein (flare) by overall clinical finding: improvement, defined as markedly effective, effective, ineffective or deteriorated at the first day and the first week post-operative day.

The "cumulative efficacy rate (which has not been defined) is stated to be 83.8% (markedly effective in 37.1%) in the bromfenac group and 67.6 % (markedly effective in 23.8%) in the pranoprofen group (p= 0.0040).

Because of the numerous deficiencies in the trial methodology, the results were regarded as being of limited value. This study could not be regarded as contributing valuable safety data either.

### STUDY 0503-CT/1

This phase I study was conducted to compare the tolerability of the sought formulation and the formulation approved in the USA and Japan.

No major differences in tolerability between the test product, the reference product and the control eyes were revealed. However, a slightly higher frequency of epithelial keratitis, burning and swelling was recorded for the new formulation than in the marketed one.

Clinically appropriate conclusions in the sought therapeutic indication were, however, impeded as the study was conducted in elderly, healthy subjects, while the test product is intended for patients with an inflammatory ocular condition. The ocular condition after a traumatic surgical procedure may impact both the efficacy and the tolerability characteristics of the drug.

In conclusion, this small tolerability trial in healthy subjects only was not considered sufficient to bridge the efficacy results obtained in the two pivotal trials. However, as the formulation has later been changed, these results were not considered of major interest.

## 2.5.3. Discussion on clinical efficacy

For both phase II studies G-04 and G-03, although the proposed concentration and dosing frequency (0.1 % BFSS-OS, BID) did not appear unreasonable, overall, the value of the 2 trials to determine the optimal dosing regimen and the optimal drug concentration was considered limited because of grave methodological and procedural shortcomings.

In the pivotal studies, there was a clear anti-inflammatory effect with the administration of bromfenac 0.1 % eye drops solution twice daily in patients with postoperative inflammation after cataract surgery, as compared to vehicle eye drops.

For the primary endpoint, the ITT analysis demonstrated a statistical significant difference between the two treatments in both trials. In the ITT population, the efficacy results are dimmed by the fact that some patients received not only the test agent but also the rescue medication at study day 15.

Statistical significance was not reached in the PP population in the ISTA-BR-CS001-WR study (p=0.0637), although convincing in the ISTA-BR-CS001-ER study (p=0.0058). However, the effect size was similar in the two populations, which supports the primary analysis.

In the absence of other anti-inflammatory medications in the ITT population *(censoring of data at the time receipt of an alternative anti-inflammatory medicine in both treatment groups*), the rate of clearance of ocular inflammation was higher for the BFSS-OS group in both studies (P<0.0001).

A large window, i.e. 16-32 hours, between the surgical procedure and the first application of trial medication may not be optimal in a clinical setting. Post-hoc analyses revealed, however, similar efficacy independent on the time from surgery to first application of the medication. Initiation of therapy prior to surgery may have a beneficial effect in the prevention/treatment of inflammation, but this was not investigated.

*Pain indication*

The effect of Yellox in treating post operative pain was not considered convincing since the effect on pain was measured within one hour of instillation of the test agent. Since BFSS-OS was administered BID, it would have been preferred to measure the effect before taking the next dose, or at least between instillations. Available data consequently failed to demonstrate that the duration of effect was longer than one hour and the clinical relevance of such limited effect duration was questioned.

The indication "pain" was removed from the sought indication as it was not supported by the provided data.

*Lack of bridging data between the sought formulation and the formulation approved in US and Japan.*

The initially sought formulation deviated from the formulation approved in the USA and Japan and used in the clinical trials. The phase I study 0503-CT/1 performed to compare the tolerability of the two formulations was not considered sufficient to bridge the efficacy results obtained in the two pivotal trials as the study was conducted in healthy subjects, but was intended for patients with an inflammatory ocular condition.

The reduced amount of BAK in the formulation was considered welcomed *per se*; however, theoretically, this reduction could impact the efficacy because of a possible diminished penetration of the active compound.

No data for efficacy of the sought formulation were provided. Based on theoretic considerations the penetration through corneal and conjunctival surface may be smaller because of the decreased concentration of BAK. In line herewith, in preclinical studies bromfenac was identified in the anterior chamber with the approved formulation, but not with the new, sought formulation.

By increasing the level of BAK to the same concentration as in the original (and tested) formulation, the major concern regardly an impaired transfer across the cornea was handled.

The remaining difference between the formulations which may have had an additional impact was the exchange from polysorbate 80 to tyloxapol.

Data on whether the additional changes to the formulation may affect the physical properties (osmolarity, pH etc.) of Yellox were presented (see Quality part). These parameters were essentially identical in the two formulations which indicated a low potential for the change of formulation to affect the tolerability.

*GCP issues*

Two GCP issues were observed during the review of the pivotal trials: inappropriate data management procedures and inadequate blinding of study medication.

During the assessment of the responses provided by the Applicant, potential quality issues during post-hoc analysis were identified. Subsequently, a GCP inspection was requested by the CHMP.

The procedures used by the Applicant during analysis were not considered completely compliant with basic GCP principles. However, the Applicant's review of the procedures and the conducted reanalyses indicated that the observed deficiencies had not significantly influenced the study results. This was considered to be satisfactory.

The GCP inspection that was performed also revealed that the pivotal studies could not be regarded as truly double-blind. However, the primary endpoint and most of the secondary endpoints relied on the degree of inflammation measured as a score defined as the anterior chamber cell score plus the anterior chamber flare score, that were considered relatively objective, especially the cell count, although a certain subjective component cannot be excluded. As the primary endpoint was based on zero scores (i.e. absence of inflammation), a possible unblinding was considered by the CHMP to have had no effect on the results.

In conclusion, it was considered unlikely that a bias favouring Yellox would have changed the results of the primary endpoint (and secondary endpoints based on cell and flare scores) to a significant extent. Further, it was considered unlikely that possible unblinding could have favoured Yellox with regard to adverse event reporting.

### 2.5.4. Conclusions on the clinical efficacy

The phase II study programme conducted in Japan in the early 1990's investigating the different concentrations of the active compound and the optimal dosing regimen bore major shortcomings and no firm conclusions could be drawn from these studies.

However, the two pivotal trials showed superior efficacy to vehicle in patients with anterior ocular inflammation subsequent to cataract extraction. The indication pain was not supported by the provided data and therefore removed from the sought indication.

A deficiency in the original dossier was the lack of data to bridge efficacy between the old formulation of bromfenac eye drops and Yellox. The formulation having been modified, all related issues have been considered solved.

## *2.6. Clinical safety*

### Patient exposure

In all studies but Croma Pharma 0503-ct/1, the safety of BFSS-OS was evaluated.

A total of 1171 patients received BFSS-OS in a clinical trial: 968 patients for postoperative inflammation (POI) following cataract surgery and 203 for another indication. All 356 patients from the U.S. were enrolled in the trials ISTA-BR-CS001-WR or -ER for investigation of POI following cataract surgery. Of the 815 patients in Japan, 612 patients were enrolled in a trial for POI following cataract surgery and 203 patients for another indication (anterior uveitis, external ocular inflammation, or

inflammation of external segment of the eye, e.g., blepharitis, conjunctivitis, keratitis, scleritis, episcleritis).

**Table 18: Exposure to BFSS OS**

| | N | **No. Patients (%)** |
|---|---|---|
| ISTA-BR-CS001-ER and ISTA-BR-CS001-WR, BFSS OS 0.1%, patients undergoing cataract surgery | 356 | 356 (100) |
| Senju studies, any BFSS OS dose, patients undergoing cataract surgery | 815 [a)] | 617 (75.7) [b)] |
| Senju studies, BFSS OS 0.1%, any indication | 815 [a)] | 664 (81.5) |

BFSS OS: bromfenac sodium sesquihydrate ophthalmic solution

a) Senju Studies G-02, G-03, G-04, G-05, G-06, G-07, G-08/09 and G-10

b) Senju studies G-02, G-03, G-04, G-05 and G-08/09, N=617.

In addition, it has been estimated that a total of approximately 20 million patients had received treatment with BFSS OS 0,1% worldwide during post-marketing, with more than 18 millions patients in Japan and around 1,3 millions patients in the United States.

In the clinical trial programme, the majority of exposed patients were from Japan, less than 400 subjects were of Caucasian origin and very few of other ethnicities. The majority of subjects were ≥ 65 years of age.

## Adverse events

In the clinical studies where bromfenac was used for treatment of post-operative inflammation following cataract surgery, a total of 3.4% of patients (6.7% in U.S. studies and 1.3% in Japanese studies) experienced one or more adverse reactions.

The adverse drug reactions (ADRs) were almost exclusively in the Eye Disorder System Organ Class. The most frequently reported (≥3 [0.3%] patients) being abnormal sensation in eye (0.5%), corneal erosion (mild or moderate) (0.4%), eye pruritus (0.4%), eye pain (0.3%), eye redness (0.3%), iritis (0.3%) and macular oedema (0.3%).

The proportion of patients with iritis was significantly lower in the bromfenac group (7.0%, 25/356) than in the placebo group (18.1%, 31/171) (P=0.0001). Frequently reported AEs (≥5% of patients), which showed a two- to five-fold lower incidence in the bromfenac group than in the vehicle group, included eye pain (4.2% for bromfenac versus 11.7% for placebo), eye redness (2.2% versus 7.6%, respectively), conjunctival hyperaemia (2.2% versus 11.1%, respectively), photophobia (2.0% versus 11.1%), visual acuity reduced (1.7% versus 5.8%), and conjunctival oedema (1.4% versus 5.3%). There was no AE reported for ≥2% of patient in either group, which showed a two-fold or higher incidence in the bromfenac group than in the placebo group.

The systemic AEs were very few and, in studies –WR and –ER, consisted essentially of few cases with nasopharyngitis and headache. In the Japanese studies there were isolated reports of systemic AEs. None of them had clear relation with the treatment.

## Serious adverse event/deaths/other significant events

In the pivotal trials no SAE was reported during study ISTA-BR-CS001-WR. In study ISTA-BR-CS001-ER, a SAE was reported for 2/198 (1.0%) patients in the bromfenac group with cardiac arrest and with cellulitis of the left foot secondary to a hammer toe surgery, and 1/98 (1.0%) patient in the placebo group with pyrexia. None of the events involved the study eye, and none was considered to be treatment-related.

One death was reported during study ISTA-BR-CS001-WR in the BFSS-OS group; the patient was hospitalised for a severe stroke nine days after dosing with BFSS-OS was completed, and died 19 days later, 28 days after the last dose of BFSS-OS. The event was reported by the investigator as not related to test agent. There was no death reported in study ISTA-BR-CS001-ER.

## Laboratory findings

Bromfenac was originally developed as an oral formulation for short-term analgesia and approved in the USA. Subsequently, the drug was voluntarily withdrawn from the market due to hepatotoxicity. No relevant laboratory abnormalities would be expected from an NSAID to be administered topically since the systemic exposure of bromfenac eye drops is expected to be very low. As a precaution, the Applicant has set focus on hepatic enzymes and included such analysis in the majority of studies. No specific findings associated with changes in liver function tests (AST, ALT, bilirubin etc.) were identified and there have been no related post-marketing reports.

## Safety in special populations

The safety in special populations has not been investigated.

In the pivotal studies, the analysis of adverse events was based on the intrinsic factors age and gender. No gender differences were apparent in the nature or incidence of ocular AEs, irrespective of causality. Since cataract mainly is a condition in an elderly population, the majority of subjects in the clinical trials were ≥ 65 years old. There were few apparent differences in the nature or incidence of ocular AEs, irrespective of causality between the age groups.

There was essentially no data from the paediatric population and no experience during pregnancy. There was also no data from subjects with a hepatic impairment.

## Safety related to drug-drug interactions and other interactions

No formal clinical interaction studies with BFSS-OS and other ophthalmic NSAID solutions have been conducted. In the course of clinical studies, BFSS-OS was commonly used in combination with ophthalmic antibiotics with no untoward effect.

## Discontinuation due to adverse events

In the pivotal trials 11/356 patients (3.1%) in the bromfenac group and 34/171 patients (19.9%) in the vehicle group discontinued treatment because of adverse events. The proportion of patients who were withdrawn because of an adverse event was larger in the placebo group than in the active therapy group. This may be a reflection of the inborn post-cataract surgery inflammation condition, which is naturally more pronounced with a vehicle therapy.

## Post marketing experience

There is no post-marketing data available for Yellox. However, an estimate of 20 millions patients were treated with BFSS OS 0,1% in Japan and United States.

The most frequently reported ocular AEs were eye pain/ache/irritation (16 patients), blepharitis (15 patients), corneal erosion (13 patients), keratitis superficial diffuse (12 patients), corneal epithelium defect (11 patients), corneal ulcer (10 patients), corneal epithelium disorder (8 patients), corneal perforation/melt (6 patients), and abnormal sensation in eye (6 patients).

In term of serious adverse reactions (SARs), corneal erosion was reported for a total of 13 patients (3 serious) during post-marketing experience from 2000-2009. All cases were reported in Japan.

Corneal perforation/melt was reported for a total of 6 patients (6 serious) (1 recovered with sequelae, 2 recovered, 2 not recovered, 1 unknown outcome). Three of the cases were from Japan and 3 from the United States.

No deaths have been reported post-marketing.

## 2.6.1. Discussion on clinical safety

The total size of the data base for controlled clinical studies conducted in Western populations was limited, as only the two pivotal trials contribute such data. In total, only 527 patients were included, of who 356 received bromfenac eye drops. Including the Japanese population, more than 1200 subjects were exposed to bromfenac eye drops during the development programme. According to ICH E5, since this is a compound that acts locally, it is unlikely that it will be affected by intrinsic ethnic factors that may affect the safety of the drug. Overall, the exposed patient population was considered sufficiently representative for the target population.

The maximum duration of exposure has not been precisely determined in the dossier, but there were no firmly stated safety data beyond 2 weeks, which was considered relatively short. A limited duration of treatment of 2 weeks is therefore recommended (section 4.2 of the SmPC).

The main concern with topical, ocular NSAIDs is the potential adverse effect on the cornea, especially in cases where the treatment duration is prolonged or if the cornea is compromised. There were no serious corneal adverse events in any of the studies. However, the majority of serious ADRs reported post-marketing consisted of corneal complications, including extremely rare, but potentially sight threatening cases of corneal ulcers and perforations. Information on the risk for corneal complications has been included in section 4.4 of the SmPC.

Evaluations included a comprehensive battery of examinations, both ocular and systemic, although not uniformly conducted in all studies. Laboratory examinations with focus on hepatic toxicity were performed in almost all studies.

No specific findings associated with changes in liver function tests, but since only subjects without any changes in liver function tests (WHO liver function toxicity grade < 1) were included in the studies, a risk for an induction of hepatic toxicity could not be excluded in pre-disposed subjects.

Due to the low systemic exposure, there is no relevant risk for systemic drug interactions. No drug interactions were reported in any clinical study involving BFSS-OS administered in conjunction with other ophthalmic medications such as antibiotics and anaesthetics. However, there was no information on the safety of bromfenac eye drops used in conjunction with corticosteroid eye drops. As NSAID,

bromfenac may interact with topical corticoids. The warning that concomitant use of Yellox and topical steroids is not recommended has been included in section 4.4 of the SmPC.

There were no adequate data from the use of bromfenac in pregnant women and therefore the potential risk for human is unknown. Since the systemic exposure in non-pregnant women can be considered negligible after treatment with bromfenac, the risk during pregnancy was considered low. However, studies in animal showed reproductive toxicity and prostaglandin biosynthesis-inhibiting medicinal products have a known effect on the foetal cardiovascular system. The use of bromfenac during the third trimester of pregnancy should therefore be avoided, unless the benefit outweighs the risks. This has been addressed in the SmPC.

## 2.6.2. Conclusions on the clinical safety

Treatment with BFSS-OS was well tolerated and there were few adverse events. Besides the important, but extremely rare risk for corneal complications, there were no safety concerns with Yellox.

## *2.7. Pharmacovigilance*

## Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

## Risk Management Plan

The MAA submitted a risk management plan

**Table 19: Summary of the risk management plan**

| **Safety Concern** | **Proposed pharmacovigilance activities (routine and additional)** | **Proposed risk minimisation activities (routine and additional)** |
|---|---|---|
| **Important identified risks**: | | |
| Corneal epithelial events<br>Corneal erosion<br>Corneal perforation<br>Corneal epithelial disorder / defect<br>Corneal ulcer<br>Corneal infiltrates<br>Corneal scar | Routine pharmacovigilance practices.<br>To be closely monitored in the RMP and PSURs. | SmPC, Section 4.8<br>• terms listed as adverse reactions<br>• precaution<br>*"Patients with evidence of corneal epithelial breakdown should immediately discontinue use of Yellox and should be monitored closely for corneal health"*<br>SmPC, Section 4.4, Precautions<br>*"Concomitant use of NSAIDs and topical steroids may increase the potential for healing problems."*<br>*"In susceptible patients, continued use of topical NSAIDs, including Yellox 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."*<br>*" ...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."* |
| **Important potential risks** | | |
| Scleral adverse events<br>Scleromalacia | Routine pharmacovigilance practices.<br>To be closely monitored in the RMP and PSURs. | SmPC, Section 4.8<br>• term listed as adverse reaction |
| Infections of the eye<br>Endophthalmitis<br>Eye infection<br>Corneal infection | Routine pharmacovigilance practices.<br>To be closely monitored in the RMP and PSURs. | SmPC, Section 4.4, Precaution<br>*"An acute ocular infection may be masked by the topical use of anti-inflammatory medicinal products."*<br>PIL, Section 5<br>*"Discard the bottle 4 weeks after first opening to prevent infection even if there is solution remaining."* |
| Events related to a potential increased risk of bleeding<br>Haemorrhagic retinopathy<br>Conjunctival hyperaemia<br>Eyelid bleeding<br>Epistaxis | Routine pharmacovigilance practices. | SmPC, Section 4.8<br>• terms listed as adverse reactions<br>SmPC, Section 4.4, Precaution<br>*"There have been reports that ophthalmic NSAIDs may cause increased bleeding of ocular tissues (including hyphaemias) 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."* |
| Events related to eye discomfort<br>Eye pain<br>Eye pruritus<br>Eye irritation<br>Eye redness<br>Abnormal sensation in eye<br>Ocular discomfort<br>Photophobia<br>Eye discharge | Routine pharmacovigilance practices. | SmPC, Section 4.8<br>• terms listed as adverse reactions |
| Visual acuity events<br>Visual acuity reduced<br>Vision blurred | Routine pharmacovigilance practices. | SmPC, Section 4.8<br>• terms listed as adverse reactions |
| Respiratory adverse events<br>Asthma<br>Cough<br>Nasal Sinus drainage | Routine pharmacovigilance practices. | SmPC, Section 4.8<br>• terms listed as adverse reactions<br>SmPC, Section 4.3, Contraindication<br>*"Yellox must not be used in patients with known hypersensitivity to bromfenac, to any of the excipients, or to other non-steroidal anti-inflammatory medicinal products (NSAIDs). Like other 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"*<br>SmPC, Section 4.4, Precaution<br>*"Yellox contains sodium sulphite which may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in susceptible patients.* |

| | | |
|---|---|---|
| | | *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 medicinal products and potential risks and benefit should be carefully evaluated"* |
| Swelling/oedema adverse events<br>Face swelling<br>Eyelid oedema | Routine pharmacovigilance practices. | SmPC, Section 4.8<br>• terms listed as adverse reactions<br>SmPC, Sections 4.3 and 4.4<br>• as described for respiratory adverse events |
| **Important missing information** | | |
| Concomitant use of topical corticosteroids | Routine pharmacovigilance practices. | SmPC, Section 4.4, Precautions<br>*"Concomitant use of NSAIDs and topical steroids may increase the potential for healing problems "*<br>*"Concomitant use of ophthalmic corticosteroids with NSAIDs is not recommended, as this combination may lead to a higher risk of corneal adverse events."* |
| More than 15 days of treatment with BFSS OS | Routine pharmacovigilance practices. | SmPC, Section 4.2, Posology<br>*"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 "* |
| Potential effect on hepatic function in patients with impaired liver function | Routine pharmacovigilance practices.<br>Will be monitored in RMP and PSURs. | n.a. |

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

## User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

## *2.8. Benefit-Risk Balance*

## Benefits

- Beneficial effects

Two pivotal clinical studies conducted after the same protocol, ISTA-BR-CS001-ER and ISTA-BR-CS001-WR, contributed to efficacy data to the sought indication. Those studies were randomised multi-centre, double-masked, parallel studies, investigating the efficacy and safety of topical Bromfenac ophthalmic solution 0.1 % versus placebo, for treatment of ocular inflammation following cataract surgery.

Patients were subjects scheduled for unilateral cataract surgery with posterior chamber intraocular lens implantation. A summed score of ≥ 3 for anterior chamber cells (scale 0-4) and flare (scale 0-4) at the baseline examination (visit 1, study day 1) was required. The therapy was scheduled for up to 14 days The primary endpoint was the proportion of patients in the ITT group with cleared ocular inflammation in the study eye at visit 4 (day 15).

The results of those two pivotal studies showed superior efficacy to placebo, in patients with anterior ocular inflammation subsequent to cataract extraction.

- Uncertainty in the knowledge about the beneficial effects.

Two major GCP issues were observed during the review of the pivotal trials: 1) Inadequate blinding of study medication; and 2) Inappropriate data management procedures.

With regards to the impact of the lack of a strict double-masked trial conduct, it is considered unlikely that a bias favouring Yellox would have changed the results of the primary endpoint (and secondary endpoints based on cell and flare scores) to a significant extent. Further, it is considered unlikely that possible unblinding could have favoured Yellox with regard to adverse event reporting.

The concerns pertaining to the GCP issues with non-compliance to the main principles for data management in clinical trials for traceability of source data during the procedures of data verification of the data source have been sufficiently addressed. There were no indications that the deficiencies observed significantly influenced the study results.

There was insufficient information to conclude on whether the efficacy data with the originally sought formulation, BFSS-OS could be extrapolated to Yellox since the small tolerability trial in healthy subjects was not considered useful to bridge the efficacy results obtained in the two pivotal trials, and the rabbit pharmacokinetic study (CRO 28) comparing the ocular penetration of the old formulation and Yellox lacked assay sensitivity. However, the formulation has been amended and these concerns are no longer considered valid.

It was discussed that the large window, i.e. 16-32 hours, between the surgical procedure and the first application of trial medication may not be optimal in a clinical setting. Post-hoc analyses revealed, however, similar efficacy independent on the time from surgery to first application of the medication. Initiation of therapy prior to surgery may have a beneficial effect in the prevention/treatment of inflammation, but this was not investigated.

Overall, the claimed therapeutic indication "pain" was not supported by the provided data. Since this part of the sought therapeutic indication has been deleted, the problem was considered solved.

## Risks

- Unfavourable effects

The reported adverse events pattern is not concerning, either as regards the frequency or the nature of ocular adverse events. A significant post-marketing experience with an estimate of over 20 million exposed patients was reassuring.

A main concern with topical, ocular NSAIDs is the potential risk for adverse effect on the cornea, especially in cases where the treatment duration is prolonged or if the cornea is compromised. This risk is relevant also for Yellox as there are post-marketing reports of such complications including extremely rare, but potentially sight-threatening cases of corneal ulcers and perforations. The same

risk is evident in case of off-label use, for example after corneal refractive procedures, or if used long-term in other ocular inflammatory conditions like blepharitis and anterior uveitis.

- Uncertainty in the knowledge about the unfavourable effects

Including the Japanese population, more than 1200 subjects were exposed to bromfenac eye drops during the development programme. However, the quality of the Japanese data might be questioned due to presumed differences in traditions in collection of safety data.

Although most Japanese studies contained a representative patient population, surprisingly few adverse events were reported from these studies and there are uncertainties regarding the quality of reporting and whether this will affect the overall adverse event profile of Yellox.

The exact duration of treatment in some Japanese studies was not identifiable in the dossier - the intended treatment duration was 2 weeks in the phase II studies and in the pivotal trials, but a considerable, though not identifiable, part of the study population received longer therapy. With these uncertainties, the total exposure is rather limited.

Approximately one third of the BFSS-treated population still had signs of a post-operative inflammation after 14 days treatment and it cannot be excluded that Yellox will be used for more than 2 weeks in this subpopulation. Since the experience from longer-term treatment is limited, the magnitude of the risk for corneal complications in case of extended use is not characterised. However, with the SmPC text in section 4.2: "The treatment should not exceed 2 weeks as safety data beyond this is not available", this has been addressed satisfactorily.

Bromfenac was originally approved in the US as an oral formulation for short-term analgesia, but withdrawn from the market due to hepatotoxicity associated with long-term use. No relevant abnormalities in hepatic enzymes were identified in the studied population and there have been no such related post-marketing reports.

## Benefit-risk balance

- Importance of favourable and unfavourable effects
    - Clinical context

Presumingly, it would have been in the best interest of the patients to start therapy before surgery, or at least as early as possible after surgery. However, such recommendations are not supported by the study data. The wording in section 4.2 of the SmPC "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" is in accordance with the pivotal clinical studies.

- Benefit-risk balance

The two pivotal trials showed superior efficacy to vehicle in patients with anterior ocular inflammation subsequent to cataract extraction. The safety and tolerability pattern does not raise major concerns, neither the frequency nor the nature of ocular adverse events. A reassuring and significant post-marketing experience with an estimate of over 20 million exposed patients adds to a positive picture.

Systemic or serious adverse events are not a prominent issue. However, the limited experience with a treatment exposure exceeding 2 weeks is a clear limitation.

### 2.8.1. Discussion on the benefit-risk balance

Overall, the benefits encompassing superior efficacy towards placebo in the treatment of postoperative ocular inflammation following cataract extraction in adults are considered to outweigh the risks.

### 2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product
- no additional risk minimisation activities were required beyond those included in the product information.

## *2.9. Recommendation*

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the benefit-risk balance of Yellox in the treatment of postoperative ocular inflammation following cataract extraction in adults was favourable and therefore recommended the granting of the marketing authorisation.