19 December 2013
EMA/13480/2014
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Izba

International non-proprietary name: travoprost

Procedure No. EMEA/H/C/002738/0000

## Note

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

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# Product information

| | |
|---|---|
| Name of the medicinal product: | Izba |
| Applicant: | Alcon Laboratories (UK) Ltd<br>Frimley Business Park<br>Frimley<br>Camberley<br>GU16 7SR<br>UNITED KINGDOM |
| Active substance: | travoprost |
| International Nonproprietary Name: | travoprost |
| Pharmaco-therapeutic group (ATC Code): | Travoprost<br>(S01EE04) |
| Therapeutic indication(s): | Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma |
| Pharmaceutical forms: | Eye drops, solution |
| Strengths: | 30 µg/ml |
| Routes of administration: | Ocular use |
| Packaging: | bottle (PP) |
| Package sizes: | 1 bottle and 3 bottles |

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# List of abbreviations

APCI-MS: Atmospheric pressure chemical ionization mass spectroscopy

BAK: Benzalkonium Chloride

BCS: Biopharmaceutical Classification System

BID: Twice daily

CHMP: Committee on Human Medicinal Products

CPMP: Committee for Proprietary Medicinal Products

EMA / EMEA: European Medicines Agency

ERA: Environmental Risk Assessment.

ERG: Electroretinogram

FTIR: Fourier transform infrared

h or hr: Hour/s

HPLC: High Performance-Liquid Chromatography

HPLC-MS : High pressure liquid chromatography with mass spectrometry detection

HPLC-UV : High pressure liquid chromatography with ultraviolet detection

ICH: International Conference on Harmonisation

IOP: Intraocular Pressure.

ISO: International Organization for Standardization

IR: Infrared

IM: Intramuscular

iv: Intravenous

Kg: Kilogram

KF: Karl Fisher titration

LC-MS/MS: Liquid Chromatography-Tandem Mass Spectrometry

Ltd: Limited

µg: Micrograms

µM: Micromolar

MAA: Market Authorisation Application

mcg: Micrograms

mg: Miligram

min: Minutes

mL: Milliliter

MPE: Mean Photo Effect

MRHD: Maximal Recommended Human Dose

N: Number

NA: Not Applicable

ng: Nanogram

nM: Nanomolar

NMR : Nuclear Magnetic Resonance

NOAEL: No Observed Adverse-Effect Level

NOEL: No Observed Effect Level

NZW: New Zealand White

OECD: Organisation for Economic Co-operation and Development

PBT: Persistence, Bioaccumulation and Toxicity.

Ph.Eur.: European Pharmacopoeia

PIF: Photo-Irritancy Factor

PP: Polypropylene

QD: Once a Day

RH: Relative Humidity

SD: Sprague Dawley

SmPC: Summary of Product Characteristics

sPP: syndiotactic polypropylene

SWP: Safety Working Party

UK: United Kingdom

USP: United States Pharmacopeia

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Alcon Laboratories (UK) Ltd submitted on 5 December 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Izba, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 May 2012. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication:

Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma.

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

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Travoprost was considered to be a known active substance.

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 tests or studies.

***Information on Paediatric requirements***

Not applicable

***Information relating to orphan market exclusivity***

***Similarity***

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

***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 MA application.Travoprost is already authorised in Travatan 40 micrograms/ml eye drops, solution with the indication to decrease of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma (Commission Decision 27/11/2001) and in combination with timolol in DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution indicated in adults for the decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues (Commission Decision 24/04/2006).

## *1.2. Manufacturers*

**Manufacturer responsible for batch release**

Alcon-Couvreur N.V.
Rijksweg 14
BE-2870 Puurs
Belgium

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

The Rapporteur appointed by the CHMP was Concepcion Prieto Yerro.

- The application was received by the EMA on 5 December 2012.
- The procedure started on 30 January 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 April 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2013.
- During the meeting on 30 May 2013, 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 30 May 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 23 September 2013.
- During the CHMP meeting on 24 October 2013, 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 18 November 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the

List of Outstanding Issues to all CHMP members on 12 December 2013.

- On 5 December 2013, the PRAC adopted an RMP advice and an assessment overview.
- On 19 December 2013, during their plenary meeting, 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 Izba.

# 2. Scientific discussion

## *2.1. Introduction*

Izba is a medicinal product that contains travoprost as active substance. It is intended for ocular administration and is available as eye drops, solution. Each ml of solution contains 30 micrograms of travoprost.

The therapeutic indication applied for by the applicant and approved by the CHMP is: Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma.

Izba has the same therapeutic indication and contains the same active substance as Travatan (Travoprost 40 µg/mL Eye Drops), but contains a lower amount of active substance. Alcon Laboratories (UK) Ltd, the Applicant for this MAA for Izba is also MAH for Travatan.

The posology for Izba (Travoprost 30 µg/mL eye dropssolution) is one drop once-daily topical ocular therapy. The therapeutic class is Ophthalmologicals-antiglaucoma preparations and miotics-prostaglandin analogues, the ATC Code is S01E E04. The mechanism of action is based on the fact that in the eye, prostaglandin increases the drainage of the watery fluid (aqueous humour) out of the eyeball. Izba acts in the same way and increases the flow of fluid out of the eye. This helps to reduce the pressure inside the eye.

Travoprost 40 µg/mL eye drops solution and travoprost 30 µg/mL eye drops solution are also referred to as Travoprost 0.004% Solution and Travoprost 0.003% Solution, respectively in this assessment report.

The clinical development of Travoprost 0.003% Solution was based on the body of work that had been compiled for the approval of Travoprost 0.004% BAK (preserved with benzalkonium chloride).

The safety and efficacy profile of travoprost has been demonstrated in several clinical trials, but the clinical development plan for Travoprost 0.003% Solution included 1 pivotal, Phase 3, safety and efficacy study (C-11-034). This safety/efficacy study was designed to demonstrate that the intraocular pressure (IOP)-lowering efficacy of of Travoprost 0.003% Solution is equivalent to the IOP-lowering efficacy of Travoprost 0.004% BAK, with both dosed once-daily in the evening in patients with open-angle glaucoma or ocular hypertension.

Two pack sizes are proposed for marketing; a pack of one 4 ml bottle and a pack of three 4 ml bottles. The pack sizes are consistent with the dosage regimen and duration of use.

## *2.2. Quality aspects*

### 2.2.1. Introduction

Izba is presented as eye drops, solution containing 30 microgram travoprost per ml solution. Izba is a medicinal product for multi-dose use and is preserved with polyquaternium-1 (also known as polyquad) and contains boric acid as preservative aid. Other ingredients are:

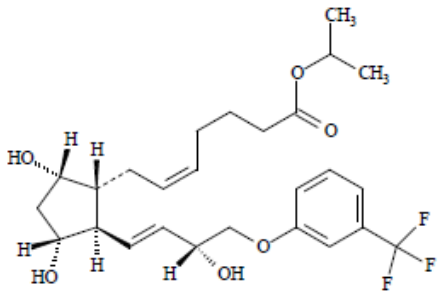
polyoxyethylene hydrogenated castor oil 40, propylene glycol, mannitol, sodium chloride, hydrochloric acid, sodium hydroxide and purified water. The qualitative composition is described in section 6.1. of the SmPC

Izba is available in oval syndiotactic polypropylene (sPP) bottles with polypropylene (PP) dispensing plugs and closures, and is presented in an overwrap. It is available in two package sizes containing respectively one and three 4 ml bottles. Each bottle contains 2.5 ml eye drops solution.

## 2.2.2. Active Substance

Travoprost is a colourless to light yellow, clear to slightly opalescent oil. It is somewhat hygroscopic, and is insoluble in water but very soluble in acetonitrile, methanol, octanol and chloroform. Its chemical names are [1R-[1α(Z),2β(1E,3R*),3α,5α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethylester and propan-2-yl 7-[3,5-dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-but-1-enyl]-cyclopentyl]hept-5-enoate.

Travoprost has the following structural formula:




The chemical structure of travoprost is confirmed by NMR, HPLC-MS, IR spectroscopy, specific optical rotation, elemental analysis and APCI-MS. Travoprost is the (+)-enantiomer of fluprostenol isopropyl ester. For confirmation of the enantiomeric purity, at least two batches were analysed by normal phase chiral HPLC-UV and compared to a racemic fluprostenol isopropyl ester standard solution.

Travoprost contains five chiral centers and is therefore optically active. Enantiomeric purity is controlled routinely by specific optical rotation. Polymorphism is not applicable as travoprost is a solution.

The applicant did not claim a new active substance status for travoprost. Travoprost is a known active substance but at the time of this opinion is neither described in the European Pharmacopoeia (Ph. Eur.) nor in the pharmacopoeia of a member state. Travoprost is described in the US pharmacopoeia.

## *Manufacture*

Travoprost is supplied by one manufacturer, details on the active substance and its manufacturing are provided in an active substance master file (ASMF).

The manufacturer synthesizes travoprost in ten steps, followed by purification.

The characterisation of the active substance and its impurities are in accordance with the relevant EU guidelines. Potential and actual impurities were well discussed with regards to their origin and characterised.

The manufacturing process is well described and adequate in-process controls are applied during the synthesis. The manufacturing process has been validated on three pilot size batches.

## *Specification*

The active substance specification includes tests for: appearance (colour and clarity), identity (IR and HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), and specific rotation (EP). All analytical methods have been adequately validated.

Tests for polymorphism and particle size distribution are not included as travoprost is a solution. Based on the results from batch analysis data, the following tests were not included in the active substance specifications: chiral purity analysis, heavy metals and silicon analysis. Chiral purity is routinely controlled in the starting material. The solvents used in the final purification step are included in the active substance specification. The travoprost active substance is a non-aqueous oil and is not tested routinely for bioburden as the microbiological quality of the travoprost stock solution (used in the manufacturing of the finished product) is routinely monitored.

Batch analysis data have been presented on two production scale batches and demonstrate that all batches comply with the proposed specifications and that the active substance can be manufactured reproducibly.

## *Stability*

The applicant has performed stability studies on three pilot scale batches of travoprost drug substance. These batches have been stored for five years at -20°C (long-term storage condition) and for 26 weeks at 4°C/35% RH (accelerated condition). The parameters tested were the same as at release, with the exception of specific rotation which is only tested at release.

Stress studies showed the drug substance to be susceptible to degradation by heat and humidity. Filling the container with nitrogen decreased the rates of degradation. Exposure to UV radiation also caused degradation. Therefore the drug substance is stored in a borosilicate glass flask, filled with a nitrogen head, sealed with a borosilicate stopper and protected from light by secondary packaging.

The stability results indicate that the drug substance is stable and justify the proposed retest period in the proposed container.

## 2.2.3. Finished Medicinal Product

### *Pharmaceutical development*

The aim was to develop a medicinal product with identical qualitative and quantitative composition to the already approved travoprost eye drops solution 0.004% (Travatan), which is preserved with polyquad, but which a reduced concentration (0.003%) of travoprost.

Izba contains the following excipients: polyoxyethylene hydrogenated castor oil 40 (solubilising / stabilising agent), propylene glycol (tonicity agent), boric acid (preservative aid/buffering agent), mannitol (tonicity agent/buffering agent), sodium chloride (tonicity agent), polyquaternium-1 solution (preservative), hydrochloric acid (pH adjustment), sodium hydroxide (pH adjustment) and purified water (vehicle).

The formulation development of Izba is based on the approved travoprost 0.004% formulation. Izba is a clear, colourless to pale yellow aqueous solution formulated at a pH of approximately 6.8 and is isotonic. Since the drug substance travoprost is an oil, polymorphism and particle size of the active compound are irrelevant. The proposed formulation contains an expected range of excipients for an aqueous eye drop solution containing a hydrophobic drug substance compound such as travoprost. The drug substance is insoluble in water, hence surfactants, solubilising agents and co-solvents are used in order to solubilise the active substance.

The excipients are identical in function and concentration to those in the authorised 0.004% Travatan formulation. The preservative system consists of polyquaternium-1 (polyquad) and boric acid. Boric acid is a preservative aid which also serves as a buffering agent. Polyquaternium-1 is a high molecular weight quaternary ammonium compound with disinfectant and preservative activity. The specifications for polyquad are the same as for the polyquad used in the approved travoprost 0.004% eye drops solution. The use of polyquad as a novel excipient was assessed and approved previously, for the 0.004% travoprost eye drops solution. On this basis the proposed formulation is considered acceptable.

Also the manufacturing process development is based on the approved travoprost 0.004% formulation. The process consists of three main steps and a risk assessment was conducted for each step. Potential critical process parameters (CPPs) were identified as well as the product quality attributed that could be affected by the CPPs. The potential CPPs were further evaluated and then ranked by means of the results of experimental studies.

The primary packaging selected for travoprost 0.003% solution is appropriately sized and is easy to squeeze due to its oval shape and deformation characteristics of syndiodactic polypropylene (sPP). Appropriate extractables and leachables tests were carried out for the proposed container closure.

### *Adventitious agents*

None of the excipients are sourced from animal materials. Satisfactory TSE/BSE certification is supplied for each excipient. The majority of excipients are synthetically produced with the exception of mannitol which is derived from a vegetable source.

## *Manufacture of the product*

Izba is a sterile medicinal product manufactured at two sites. The manufacturing process for the travoprost 0.003% solution involves three major steps: i) preparation of travoprost stock solution, ii) dissolution of the water soluble ingredients followed by addition of the travoprost stock solution and sterilization of the solution by membrane filtration and iii) aseptic filling of the sterile solution into packaging components previously sterilized by ethylene oxide.

Terminal sterilisation and steam sterilisation of the final bulk was considered but was not possible because the active is prone to degradation at these temperatures. This manufacturing process is essentially the same as that approved for the travoprost 0.004% solution (Travatan). The critical steps in the manufacturing process have been adequately identified and controlled. The in-process controls are adequate for this non-standard manufacturing process and for this pharmaceutical form.

Process validation was performed on three commercial scale batches for both sites. The process validation results demonstrate that the process is able to reproducibly produce a finished product of the intended quality.

## *Product specification*

The finished product release specifications include appropriate tests for identity (UHPLC, TLC), assay (UHPLC), impurities (UHPLC), identity and assay of boric acid (HPIC), identity and assay of polyquaternium-1 (spectrophotometric method), pH, osmolality, colour (visual examination), clarity (Ph.Eur.), particles/particulates (visual), fill volume(IPC test) and sterility (membrane filtration).

The absence of tests for residual solvents and metals has been adequately justified; no residual solvents & metals have been detected in the stability batches. The proposed finished product specification (release and shelf life) is considered satisfactorily robust and appropriate and the analytical procedures are regarded sufficiently validated.

Batch analysis data have been provided for four commercial scale batches and one clinical batch. These batches were made with travoprost sourced from both active substance suppliers and include also both finished product manufacturers. The data demonstrate that the predefined product specifications are met and that the manufacturing process is under control.

## *Stability of the product*

The stability studies were carried out on five batches including four commercial scale batches and one clinical batch, produced at both proposed finished product manufacturing sites. The four commercial scale batches were packed into the packaging materials which are intended for marketing; they were over pouched using the foil laminate secondary packaging, the clinical batch was not over pouched.

Up to 78 weeks long term stability data (at 25°C/40%RH) have been presented for the commercial scale batches, and up to 52 weeks long term stability data have been provided for the clinical batch. Furthermore, stability data have been provided for studies performed under

accelerated and intermediate storage conditions, and stress tests have been performed under refrigerated conditions, freeze/thaw cycles and after light exposure. After 6 weeks of light exposure, increase in degradation product contents is observed. Increase of degradation product content is more important for samples without secondary packaging. All other chemical or physical assay results showed no significant changes for the samples when stored under stressed conditions.

In addition, two commercial scale batches were evaluated in an in-use test, which measured the total viable microbial count of remaining product after simulating patient usage over a 30 day period. During the in-use 30 day study, the test product was stored at ambient room temperature (20-25°C), protected from light.

Furthermore, results of supportive long term stability data from the approved travoprost 0.004% w/v eye drop solution formulation have been provided for three batches stored over three years. As the composition, fill volume and packaging is identical to the travoprost 0.003% eye drop solution the stability data may be considered to be supportive for overpouched product as all batches were overpouched.

The shelf-life specifications include the same tests as the release specifications, with the exception that the following tests are not performed during stability: identity for travoprost, boric acid and polyquaternium-1 and fill volume.

Supportive stability results for additional physical tests such as: precipitate, particulate matter, package condition, foreign insoluble matter, insoluble particulate matter and weight change, as well as the microbiological test, preservative effectiveness Test were provided. The results show no significant change upon storage. Based on available stability data, the proposed shelf-life and conditions for storage as stated in the SmPC are acceptable.

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

The development of Izba was largely based on the approved travoprost eye drops solution 0.004% polyquaternium formulation, with the exception of a reduced concentration of travoprost. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate 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.

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

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

### 2.2.6. Recommendation(s) for future quality development

Not applicable.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

The Applicant submitted a full pharmacology dossier to explain the pharmacology of travoprost. Also called AL-6221, travoprost is a synthetic prostaglandin F2$\alpha$ analogue. Travoprost free acid, or AL-5848, a selective F-prostanoid (FP) prostanoid receptor agonist, used to decrease elevated intraocular pressure in ocular hypertension or open-angle glaucoma as monotherapy or as adjunctive therapy. F-prostaglandin receptor agonists increase aqueous humor outflow through the uveoscleral pathway in animal models and man.

Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its biologically active free acid. Travoprost 0.003% Solution, containing 30 μg/mL travoprost, is a sterile ophthalmic solution preserved with polyquaternium-1 (POLYQUAD).

### 2.3.2. Pharmacology

***Primary pharmacodynamic studies***

A battery of in vitro and in vivo studies has been conducted to assess the mechanism of action of this FP receptor agonist. For in vitro test systems, AL-5848 (0.1 nM to 100 μM), the free acid of travoprost, was used because of the likely lack of esterase to hydrolyze the parent compound in the test systems used.

Prostanoid receptor binding affinity tests for the free acid of travoprost AL-5848, show that AL-5848 is a selective and full agonist at the FP prostanoid receptor. AL-5848 exhibited no significant receptor activity for a battery 32 physiologically relevant receptors at concentrations up to 10 μM.

In vivo, travoprost significantly reduced IOP in laser-induced ocular-hypertensive monkeys when administered daily (0.3 μg and 1 μg) and twice daily (0.1 μg and 0.3 μg) by topical ocular administration. Travoprost reduction in IOP peaked at ≈22 and ≈30% (for 0.1 and 0.3 μg BID doses respectively), and ≈26 and ≈29% (for 0.3 and 1 μg QD). The IOP response was sustained through 24 hours and returned to baseline by 48 hours after the last once daily instillation.

***Secondary pharmacodynamic studies***

The secondary pharmacodynamics assessment includes the effects of travoprost on optic nerve head blood flow and on the retina via flash electroretinogram (ERG) in rabbits. Travoprost

increased optic nerve head blood flow, which is considered to be a possible component in the etiology of glaucoma, and produced no significant changes in the ERG of Dutch-belted rabbits.

***Safety pharmacology programme***

The potential of travoprost to alter central nervous, cardiovascular, respiratory, gastrointestinal and renal systems, as well as their effects on the uterus, were examined at doses up to 30 µg/kg (equivalent to 833-fold the maximal recommended human dose (MRHD)). The findings noted in the safety pharmacology studies with travoprost or its free acid, AL-5848 are consistent with the known pharmacology of PGF2α.

Travoprost produced no significant effects on the central nervous, renal or respiratory system. Furthermore, travoprost showed no significant effects on cardiac repolarisation.

At high doses (10 µg/kg), significant effects on cardiac contractility, blood pressure and left ventricular pressure were observed in dogs. However, these effects were observed at plasma concentrations higher than those achieved clinically at IOP-lowering doses, with a wide safety margin (278-fold the MRHD).

In guinea pigs, a small but statistically significant increase in respiratory rate was observed following 10 µg/kg travoprost treatment. The changes, although were statistically significant, could be considered not biologically relevant since they were transient in nature (2-8 min in duration) and did not translate into changes in airway resistance or dynamic lung compliance.

Travoprost increase gastrointestinal propulsion in a dose-dependent manner in mice, consistent with the known agonist activity of AL-5848 on FP prostanoid receptors. However, these GI effects are not expected at clinically relevant doses.

Prostaglandins are recognized effectors of uterine function. AL-5848 induced concentration-dependent uterine contractions in isolated, diethylstilbestrol-primed rat uteri, consistently with the known pharmacology of PGF2α. These uterine contractions were found to occur at concentrations of 3 nM to 1 µM, (translating to doses from 6 to 20,000-fold higher than plasma levels achieved clinically).

***Pharmacodynamic drug interactions***

AL-5848 was essentially inactive at a variety of common central and peripheral receptors - e.g. adenosine, alpha-1 adrenergic, alpha-2 adrenergic, beta-adrenergic, muscarinic, nicotinic, dopamine, serotonin, melatonin and glutamate receptors. Therefore, travoprost is unlikely to interact adversely with other glaucoma agents or with other receptor-mediated pharmacologic agents.

## 2.3.3. Pharmacokinetics

The absorption, distribution, metabolism and excretion of travoprost have been studied in Sprague-Dawley rats by administration of [3H]-travoprost by the oral, intravenous and subcutaneous routes, and in New Zealand White (NZW) rabbits by the topical ocular and intravenous routes and Cynomolgus monkeys by intravenous route. For systemic

pharmacokinetic studies non-labelled travoprost was administered to SD rats by the intravenous and subcutaneous routes and to Cynomolgus monkeys intravenously.

The analytical method used for non-labelled studies was fully validated for precision, accuracy and stability for each species and matrix. The procedure employed a LC/MS/MS method for detection of the active free acid AL-5848, which is formed by rapid hydrolysis of travoprost in vivo and in vitro.

The pharmacokinetic studies showed that AL-6221 is absorbed and rapidly hydrolyzed by esterase enzymes to its free acid AL-5848, the pharmacologically active form. Therefore, the AL-5848 levels are substantially higher than AL-6221 levels: in monkey plasma AL-5848 concentrations were generally 4-fold higher than AL-6221 concentrations.

Plasma concentrations of AL-5848 declined rapidly and in a biphasic manner following intravenous administration of AL-6221 in rats and monkeys and with t1/2 of 16 and 36 minutes, respectively.

Following subcutaneous administration, maximal plasma concentrations and exposure to AL-5848 increased in a dose-proportional manner.

The study in rats also showed that travoprost is poorly absorbed following oral dosing. The bioavailability of AL-5848 after oral doses were both low (<3 to 6%).

In vitro binding of AL-5848 to rat, monkey and human plasma proteins was similar between species at approximately 80% and independent of concentrations up to 100ng/ml.

Tissue distribution studies of travoprost in rats showed highest concentrations in kidney, liver, lung and plasma. Radioactivity concentrations decreased over the first hours, but were still detectable in most tissue through 72 hours after multiple dose regimen. In pregnant rats, radioactivity was measured in amniotic fluid and fetal tissues with highest fetal tissue concentrations in liver and lung, which were approximately 2-4% of that in maternal plasma.

The metabolism of travoprost and AL-5848 was studied in in vitro and in vivo in rats and cynomolgus monkeys. AL-6221 is rapidly de-esterified by plasma esterases enzymes to AL-5848, its pharmacologically active carboxylic acid form. Travoprost and AL-5848 are rapidly metabolised, following similar pathways to that of endogenous prostaglandin-F2$\alpha$, which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and $\beta$-oxidative cleavages of the upper side chain. This is based on the non-clinical metabolism studies and studies reported in the literature on the metabolism of prostaglandins in humans.

In rats, travoprost is rapidly excreted, with 34% and 74% being recovered in urine and faeces, respectively. Travoprost undergoes extensive biliary excretion and is excreted in the milk of lactating rats.

No pharmacokinetics drug interaction studies with travoprost and other medicinal products have been conducted and this has been mentioned in the SmPC section 4.5.

## 2.3.4. Toxicology

The Applicant submitted a toxicology package that was also presented for marketing authorization applications for other formulations of travoprost previously authorised. No new

toxicology studies were conducted with Travoprost 0.003% Solution. The toxicology package was acceptable to the CHMP.

***Single dose toxicity***

The topical administration of travoprost 0.004% at single dose demonstrated that the product is well tolerated in rabbits. The intravenous administration of AL-6221 in the rat was lethal for 4/8 males at 100 mg/kg. However, the same dose in the mouse did not produced deaths. The toxicity of travoprost following intravenous single dose appears to be consistent with other prostanoid agents.

***Repeat dose toxicity***

The effects of travoprost following the repeat dose administration have been studied in mice, rats, rabbits and monkeys. In mice, AL-6221 was dosed intravenously and intraperitoneally while in rats, the product was administered intravenously and subcutaneously. Both in rabbits and monkeys, travoprost was administered by topical route.

In mice, travoprost was administered intravenously at 100, 300 and 1000 μg/kg/day for 3 months. Non dose-related mortality and slight reductions in haematological parameters were observed at high doses. No recovery period was included in this study. The microscopic examination of bone revealed a high, dose-related incidence of hyperostosis and endosteal fibrosis in the femur and sternum, which may have caused a reduction of bone marrow space leading to the haematologic changes observed. This appeared to be supported by the increased extramedullary haematopoiesis seen in the liver and spleen.

In rats administered subcutaneously up to 100 μg/kg/day for 6 months, slight reductions in haematological parameters were detected and bone hyperostosis and endosteal fibrosis were observed at ≥30 μg/kg/day.

In rabbits given topical ocular doses of Travoprost 0.004% BAK (10 to 100μg/mL) two or three times daily for 6 months, no signs of ocular irritation or systemic toxicity were found and neither macroscopic nor microscopic changes in the eyes or adnexa were observed.

Based on the repeated dose studies in rodents, bone was considered the target organ, with a no effect level of 10μg/kg/day. This dose is approximately 278 times the proposed recommended clinical dose. The effects on bone were not observed in mice at similar and higher dose levels and were not detected in rabbits or monkeys. Thus, it is considered unlikely that the proposed ophthalmic use of Travoprost 0.003% solution will induce any bone-related effects.

***Genotoxicity***

The standard battery for genotoxic assessment has been conducted in six studies, four in vitro and two in vivo. No evidence of mutagenic activity was observed in the bacterial reverse mutation assay. Travoprost was considered to be negative without metabolic activation and equivocal with metabolic activation in the mouse lymphoma mutation assay. Taking into account the negative results in the bacterial and in the two in vivo assays and the negative result

obtained in the second mouse lymphoma forward mutation assay, the risk of mutagenic potential for travoprost can be considered low.

***Carcinogenicity***

The carcinogenicity package provided is the same as previously evaluated for the other travoprost formulations. No further studies have been performed since carcinogenicity was discussed in previous marketing authorization applications of travoprost. The carcinogenic potential of travoprost was investigated in two-year studies in mice and rats, administered by subcutaneous injection, at doses up to 100µg/kg/day. In these carcinogenicity studies, maximal mean concentrations in the high dose group ranged from 4.18 to 6.96 ng/ml in mice and 8.8 to 10.8 ng/ml in rats.

In the rat study, statistically significant increases in some tumour types, as pheochromocytoma, skin fibroma, squamous cell papilloma and uterine granuloma cell tumour, were present by some statistical measures. These tumour findings were considered to be incidental, and not related to treatment with travoprost.

***Reproduction Toxicity***

In embryo-fetal development toxicity study performed in mice, only a quantifiable exposure to AL-5848 was observed in 4 of the 8 high-dose study animals, ranged from 0.104 to 0.126ng/mL. All other samples obtained from the other doses were below the limit of quantitation.

No new developmental and reproductive studies were conducted with Travoprost 0.003% Solution. Only studies to support other formulations of travoprost have been submitted.

In the fertility and early embryonic development toxicity studies, the effects on reproduction, as the reduced viable foetuses per dam observed, were the ones expected given the pharmacological activity of travoprost.

Regarding the embryo-fetal development toxicity study mice administered with travoprost from GD 6 to 16, an increase in the percentage of early resorption and post-implantation loss and reductions in the number of dams with viable foetuses, live foetuses per dam and fetal body weight were observed at 1 µg/kg/day. The no effect level for embryo-fetal toxicity was reported to be 0.3 µg/kg/day.

In the prenatal and postnatal development studies, including maternal function, performed in rats, AL-6221 administered by subcutaneous doses produces effects in dam rats at > 0.12 µg/kg/day

No studies in juvenile animals have been submitted.

***Toxicokinetic data***

Toxicokinetics were assessed during topical ocular administration of travoprost in rabbits over a period of 3 and 9 months and in the cynomolgus monkey over a period of 12 months after topical ocular application of the medicinal product in the pharmaceutical form proposed for therapeutic

use. Other toxicokinetic data were obtained from carcinogenicity studies and embryo-fetal development toxicity study.

In rabbits, there was measurable systemic exposure to AL-5848 following topical administration of AL-6221 at the highest dose and in a small number of samples in the middle dose, although there were also many doses where the exposure was below the assay quantitation limit. No evidence of sex-related differences in AL-5848 plasma concentrations was demonstrated. Mean steady-state AL-5848 concentrations showed an approximately dose-proportional increase over the dose range.

In monkeys, a quantifiable exposure to AL-5848 in all three AL-6221 treatment groups was reported. A minor sex related difference (male AL-5848 plasma concentrations those of females) at the high dose was seen, but the trend was not consistent across doses.

***Local Tolerance***

The local tolerance of AL-6221 has been assessed in the context of single-dose and repeat-dose toxicity studies. No relevant local toxic effects were observed in rabbits and monkeys after topical administration of travoprost.

***Other toxicity studies***

Regarding the potential phototoxic of travoprost, the product is considered non-phototoxic since the mean photo effects (MPEs) were 0.022 and 0.007, and the PIFs were 1.12 and 1.08, in the Neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts. Also travoprost could be considered a non-sensitizer according to a sensitization study conducted in guinea pigs.

No immunotoxicity, dependence studies have been performed and studies in metabolites have been submitted. This is considered acceptable.

Impurities of travoprost 0.003% solution have not been evaluated. However, the Applicant submitted two studies in which the impurities of AL-6221 were assessed. Such impurities (e.g.: epoxide impurity or AL-12535 observed at concentrations of up to 0.5% of drug substance) were well tolerated and produced no signs of ocular irritation or treatment related toxicity.

***Ecotoxicity / environmental risk assessment***

A Phase I calculation of Predicted Environmental Concentration (PEC) assessment according to the “Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00)” has been performed for Travoprost 0.003% Ophthalmic Solution.

Therefore, $PEC_{surfacewater}$ in Phase I for travoprost results is 0.000000009 mg/L or 0.009 µg/L.

As the $PEC_{surfacewater}$ value is below the 0.01 µg/L action limit value, a Phase II environmental effect analysis is not needed. Travoprost is considered unlikely to represent a risk for the environment following its prescribed use and no further action is required under the Committee for Medicinal Products for Human Use (CHMP) “Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00)”.

**Table 1. Summary of main study results**

| **Substance (INN/Invented Name): Travoprost / Izba** | | | |
|---|---|---|---|
| **CAS-number (if available):** | | | |
| ***PBT screening*** | | Result | **Conclusion** |
| *Bioaccumulation potential*- log $K_{ow}$ | OECD123 … | | See below and Discussion on non-clinical aspects for further clarification |
| ***Phase I*** | | | |
| **Calculation** | **Value** | **Unit** | **Conclusion** |
| PEC $_{surfacewater}$ , default or refined (e.g. prevalence, literature) | 0.009 | µg/L | Not above threshold |
| Other concerns (e.g. chemical class) | | | No |

The log $K_{ow}$ value according to Partition Coefficient (n-octanol/water) OECD Guideline 123 for testing of chemicals "Partition Coefficient (1-Octanol/Water): Slow-Stirring Method", was provided by the Applicant. This value for travoprost is 4.483. However, the study that ascertained this value was not carried out according to the criteria set out in the relevant OECD Guideline. Therefore, the log $K_{ow}$ value for travoprost of 4.483 as determined in this study is questionable. In order to conclude on the exact log $K_{ow}$, its value should be determined strictly according to the guideline of the method chosen.

If the log $K_{ow}$ value obtained for the product would be higher than 4.5, according to "*Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00)*" and "*Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/44609/2010)*", travoprost should be screened by the MAH in a step-wise procedure for persistence, bioaccumulation and toxicity.

## Discussion on non-clinical aspects

Izba is in the pharmacological class of PGF2α agonists that includes latanoprost, bimatoprost, and tafluprost. Ophthalmic formulations of travoprost preserved with different preservatives (Travoprost 0.004% BAK, Travoprost 0.004% sofZia, and Travoprost 0.004% PQ) are marketed in the USA and/or European Union and in the process of development have undergone extensive non-clinical and clinical testing. Travoprost 0.003% Solution is identical to the formulation of Travoprost 0.004% PQ with the exception of a lower concentration of the active ingredient, travoprost.

The same studies have been submitted as those that were provided to the marketing authorization application for Travoprost 0.004% preserved with BAK, Travoprost 0.004% preserved with sofZia, and Travoprost 0.004% preserved with polyquaternium (POLYQUAD [PQ]).

With regards to the environmental risk assessment, the available data do not allow to conclude on the potential risk of travoprost to the environment. A log $K_{ow}$ value measured according to Partition Coefficient (n-octanol/water) OECD Guideline 123 for testing of chemicals "Partition Coefficient (1-Octanol/Water): Slow-Stirring Method" was provided (4.483). However, the report provided by the Company did not meet the criteria set out in the relevant OECD Guideline.

Sections 5.3 and 6.6 of the SmPC and Section 5 of the PL include wording that adequately reflects the above and captures also data and knowledge from the originally submitted dossier for the previously authorised travatan 40 µg /ml.

### Conclusion on non-clinical aspects

Overall, the non-clinical aspects of Travoprost 0.003% have been adequately documented and meet the requirements to support this application.

No issues of concern have been detected in regards to the non-clinical information of Travoprost 0.003% Solution provided.

However, the study that ascertained the log $K_{ow}$ value for travoprost (4.483) was not carried out according to the criteria set out in the relevant OECD Guideline. Therefore, the log $K_{ow}$ value of 4.483 as determined in this study is questionable. In order to conclude on the exact log $K_{ow}$, its value should be determined strictly according to the guideline of the method chosen.

Adequate wording is included in the relevant sections of the SmPC and PL that reflect the above assessment.

## *2.4. Clinical aspects*

### 2.4.1. Introduction

The clinical development plan for Travoprost 0.003% Solution is based on one pivotal, Phase 3, safety and efficacy study (C-11-034).

- Tabular overview of clinical studies

**Table 2.5.1–2 Clinical Development Plan for Travoprost 0.003% Solution**

| Protocol Type/No. | Study Design | Subject/Patient Population | Treatment Groups | Dosing Regimen | Dosing Duration | Total No. Randomised: Total No. Exposed to Travoprost 0.003% Solution |
|---|---|---|---|---|---|---|
| **Safety/Efficacy**<br>**Phase 3 (pivotal)/**<br>**C-11-034**<br>(TDOC 0015855, 5351) | Multicenter, double-masked, randomized, active-controlled, 2-arm, parallel-group, equivalence study | Males and females of any race/ethnicity, who were 18 years of age and older, and who were diagnosed with open-angle glaucoma or ocular hypertension | Travoprost 0.003% Solution<br><br>Travoprost 0.004% BAK | 1 drop in the treated eye(s) once daily at 8 PM<br><br>1 drop in the treated eye(s) once daily at 8 PM | 3 months | 864 total:<br>442 exposed to Travoprost 0.003% Solution |

***GCP***

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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.

## 2.4.2. Pharmacokinetics

No new pharmacokinetic data were specifically generated to evaluate the absorption, distribution, metabolism and excretion of Travoprost 0.003% solution in humans. The reason why these studies were not conducted was based on rabbit ocular tissue distribution and plasma data that showed both Cmax and AUC0-6h levels were very similar following topical ocular doses of Travoprost 0.004% BAK, and with Travoprost 0.004% PQ, that is formulated in the same vehicle as Travoprost 0.003% Solution. Therefore, it was considered acceptable to expect that ocular and systemic exposure levels would be approximately dose proportionally less with Travoprost 0.003% Solution compared to Travoprost 0.004% BAK and Travoprost 0.004% PQ.

***Pharmacokinetic interaction studies***

No pharmacokinetics drug interaction studies with travoprost and other medicinal products have been conducted. This is reflected in section 4.5 of the SmPC.

## 2.4.3. Pharmacodynamics

No specific studies were conducted to evaluate the pharmacodynamics of Travoprost 0.003% Solution in humans.

***Mechanism of action***

The pharmacodynamic action of ophthalmically applied prostaglandin agonists, including travoprost, has been well characterised and no new studies have been conducted relating to the underlying mechanism of action. Travoprost is the isopropyl ester pro-drug of a potent and

selective F-prostanoid (FP) prostaglandin receptor agonist. It belongs to the pharmacological class of PGF2α agonists that includes other globally established marketed IOP-lowering agents.

***Primary and Secondary pharmacology***

Prostaglandin analogues are currently the most widely prescribed first-line ocular hypotensive agents. They exert their therapeutic effect by increasing the outflow of aqueous humour via the trabecular meshwork and uveoscleral pathways.

### 2.4.4. Discussion on clinical pharmacology

Given the available data generated for pre-existing formulations, the absence of pK or pD studies with the intended concentration was considered to be acceptable.

### 2.4.5. Conclusions on clinical pharmacology

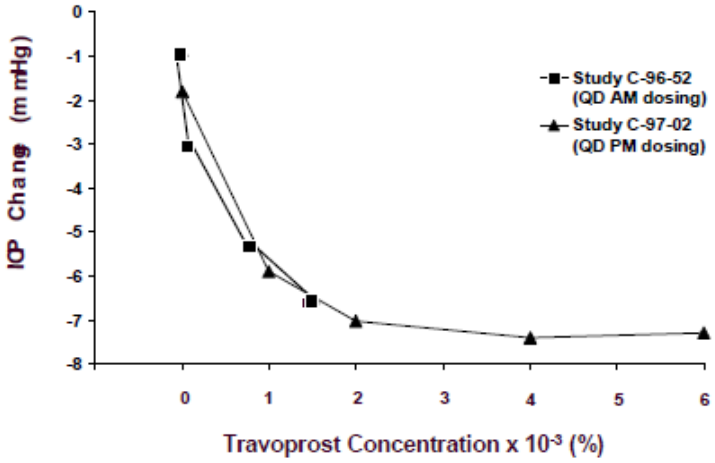
The Applicant submitted an application for a new formulation of travoprost in which the concentration of the active has been reduced to 30mcg/ml from the 40mcg/ml previously authorised (Travatan). The indications and frequency of application remain unchanged. Given the topical nature of the product, and well-characterised therapeutic characteristics of travoprost, no clinical pharmacology studies with the new formulation were conducted. Instead, the application was supported by a pivotal efficacy and safety study, as discussed below. This was considered adequate and acceptable by the CHMP.

## *2.5. Clinical efficacy*

### 2.5.1. Dose response studies and main clinical studies

The 30mcg/ml concentration in Izba represents a 25% reduction in concentration compared to currently licensed travoprost (Travatan) formulations. No dose selection study was conducted in order to find out a lower, efficacious dose. The selection of the 0.003% concentration was based on dose-response clinical studies conducted during the early development of Travoprost 0.004% BAK. Study C-96-52, and C-97-02 evaluated travoprost concentrations ranging from 0.0001% to 0.006%, and on one preclinical pharmacokinetics study including Travoprost 0.003% Solution (P-11-510).

**Figure 2.5.1–1** **Mean IOP Change from Baseline C-96-52 and C-97-02 (Intent-To-Treat Data)**




Results (mean IOP change) from both dose-response studies (intent-to-treat data) are presented. Data are pooled over visit (Days 7, 14 and 28) and time of day (8 AM, 10 AM, 12 N, 4 PM and 8 PM). All IOP changes are from least squares means and values are provided in Clinical Study Reports C-96-52 and C-97-02 contained in Module 5354.

A dose-dependent response (IOP reduction) was observed in the low dose range explored. Doses equal or higher than 0.002% reached significant (and quantitatively similar) IOP reductions. The greatest IOP lowering efficacy was shown by Travoprost 0.004%. This effect was confirmed during the Phase III. The travoprost 0.003% concentration was not specifically tested in those trials. It may be hypothesised that lower doses (e.g.: 20 μg/mL or 25 μg/mL) could have also been an option. Upon CHMP request, however, the Applicant adequately justified the safety and efficacy of the selected strength. However, in order to better address this topic, the MAH was encouraged to consider the possibility to explore the efficacy of a lower concentration product, given that studies with the 30 µg/ml dose, PD and historical clinical data indicate that there is a potential for even lower doses.

**Pivotal Study C-11-034:** A Multicenter, Double-Masked Study of the Safety and Efficacy of Travoprost Ophthalmic Solution, 0.003% Compared to Travatan in Patients with Open-Angle Glaucoma or Ocular Hypertension.

***Methods***

The pivotal study (C-11-034) was a multicentre, randomized, double-masked, parallel-group clinical trial. This study was conducted at 60 investigational centres, including 52 in the USA and 8 in EU (Sweden, Germany, Austria, Spain and Finland). In this study, the new formulation Travoprost 30 µg/ml solution preserved with polyquaternium (POLYQUAD [PQ] (study drug) was compared with Travatan 40µg/ml solution preserved with BAK (comparator).

The primary objective of this study was to demonstrate that the IOP-lowering efficacy of Travoprost 0.003% PQ-preserved (Izba) is equivalent to Travoprost 40 µg/ml BAK- preserved in patients with open-angle glaucoma or ocular hypertension.

The study was conducted in 2 phases: Phase 1 (Screening/Eligibility Phase) and Phase 2 (Treatment Phase).

After meeting all eligibility criteria, patients were randomly assigned to treatment groups within each investigational site. The use of a randomisation code to assign study drug protected against selection bias (i.e., the tendency to place patients with a greater chance of treatment success on a treatment believed to have greater efficacy). Further stratification of the randomisation (by investigational centre and 8 AM baseline IOP of the study eye) was intended to ensure balanced baseline IOP measurements between treatment groups. Patients ≥18 years of age, diagnosed of open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion component) or ocular hypertension and a mean IOP ≥ 24 mmHg at the 8 AM time point and ≥ 21 mmHg at the 10 AM and 4 PM time points at entry were recruited.

On-therapy evaluations at Weeks 2 and 6 then Month 3 were considered sufficient to monitor patient safety.

The study was double-masked, and neither the patient nor the study personnel who conducted the assessments had knowledge of the assigned treatment sequence, ensuring that the evaluations were not influenced by knowledge of the identity of specific treatments.

The choice of the reference (control) treatment is discussed “Treatments” below.

***Study Participants***

Patients with a diagnosis of open-angle glaucoma or ocular hypertension were eligible provided they met standard entry inclusion/exclusion criteria which were consistent with those applied previously in the clinical trials for Travoprost.

Entry criteria were such that randomised patients demonstrated IOP elevations (lower limit 24 mmHg at 8 am; 21 mmHg at 10 am and 4 pm) which were representative of most populations with open-angle glaucoma or ocular hypertension. They were also consistent with entry criteria selected in the pivotal studies conducted previously for all currently approved Travatan 0.004% formulations. An upper limit of 36 mmHg was chosen to avoid enrolling patients who, during the washout period, could develop IOP levels that might cause additional glaucomatous damage.

For each patient, only one eye was designated the “study eye” for analysis purposes, and this corresponded to the most severely affected one (defined as the eye with the higher IOP at 8am averaged across the two eligibility visits, or if equally affected, then the one with the higher IOP at the next time point(s). If the pressures remained equal at each of the three time-points, then the default was to designate the right eye. This approach had been accepted by regulatory authorities for previous applications and was considered acceptable by the CHMP.

The washout schedule and IOP eligibility criteria are shown in Tables 3 and 4):

**Table 3: Washout period prior to dosing**

| Ocular Hypotensive Medications | Washout Period from Screening to Eligibility 1 |
|---|---|
| Miotics and Oral/Topical Carbonic Anhydrase Inhibitors (CAIs) | ≥ 4 days |
| Alpha and Alpha/Beta Agonists | ≥ 13 days |
| Beta-Antagonists, Prostaglandin Analogues, and Fixed Combination Medicinal Products | ≥ 27 days |

**Table 4: Qualifying IOP at Eligibility Visits (1 and 2)**

| Qualifying IOP (mmHg) | | |
|---|---|---|
| Eligibility 1 and Eligibility 2Visits | | |
| 8 AM | 10 AM | 4 PM |
| 24 to 36 | 21 to 36 | 21 to 36 |

The same eye was required to qualify at each time point. The Eligibility 2 visit was conducted 3 to 8 days after the Eligibility 1 visit. Two eligibility visits were important to ensure a stable baseline for IOP, reduce the risk of regression to the mean and ensure valid assessment of IOP reduction while on treatment.

A study duration of 3 months was considered sufficient to establish the efficacy of an IOP-lowering therapy. With regard to long-term safety, there is an extensive database relating to the safety of the higher strength Travoprost (both via clinical trials with a duration up to 5 years as well as post-approval experience) and therefore longer term safety with the lower strength, 0.003%, formulation was not considered necessary.

***Treatments***

Choice of the Control Group

Travatan preserved with BAK was selected as comparator arm in the study, although this formulation is no longer marketed in the USA or the EU. This was justified by the applicant on the following basis:

- The BAK-preserved formulation served as the reference product in clinical studies supporting marketing authorisation in the EU for Travatan preserved with PQ and in the USA for Travatan preserved with SofZIA.
- The safety and efficacy of Travatan preserved with BAK has been well-established through clinical studies and over the course of >10 years' post-marketing experience.
- Travatan preserved with BAK is the only formulation that had been approved in both the EU and USA, allowing a single global multi-centre study to be conducted.

- Comparison against the original formulation (Travatan preserved with BAK) rather than the subsequent formulations preserved with PQ, avoids the potential for "bio-creep" associated with non-inferiority/equivalence trials over time that may otherwise involve progressively less effective active controls.

IOP evaluations

During the treatment phase, visits were performed at Week 2, Week 6 and Month 3 and at these visits the primary parameter, IOP, was assessed at the same time points as at Eligibility visits 1 and 2 (8am, 10am and 4pm). The timing of the visits was consistent with those used previously for the MAs of the Travoprost 0.004% formulations to allow validation with the efficacy data obtained for the higher strength products.

***Objectives***

To demonstrate that the IOP-lowering efficacy of Izba (travoprost 0.003% PQ-preserved) is equivalent to that of Travatan (travoprost 0.004% BAK-preserved) in patients with open-angle glaucoma or ocular hypertension.

***Outcomes/endpoints:***

***Efficacy***

Primary Endpoint: IOP at Week 2, Week 6, and Month 3 for each assessment time point (8 AM, 10 AM, and 4 PM)

The supportive endpoints included the change in IOP from baseline, the percent change in IOP from baseline, the percentage of patients who achieved a target IOP level of < 18 mmHg, and the percentage of patients who achieved IOP-lowering of at least 30% from baseline.

***Safety***

Adverse events, best corrected visual acuity, ocular signs, visual field function tests, central corneal thickness, ocular hyperaemia, dilated fundus exam.

***Sample size***

The sample size estimate was based upon a SD for IOP of 3.5 mmHg, a 5% chance of a Type I error, and an assumption that the population means in the 2 groups were identical. 720 patients were subsequently planned to ensure that at least 640 patients (320 per treatment group) were followed for 3 months, in order to provide:

- ≥ 99% power that a 95% 2-sided CI of the difference in IOP would fall within ± 1.5 mmHg
- ≥90% power that a 95% 2-sided CI of the difference in IOP would fall within ± 1.0 mmHg.

for the Travoprost 0.003% Solution group minus the Travatan group) at Weeks 2 and 6, and Month 3 and at assessment time points (8 am, 10 am, and 4 pm)

***Randomisation***

Patients were randomised using an Interactive Web Response System (IWRS). Randomisation was stratified, within the investigational centre, according to the 8 am baseline IOP measurement in the study eye in order to ensure baseline measurement ranges (low: 24–27 mmHg; high: 28–36 mmHg) were balanced between study drug groups.

***Blinding (masking)***

This was a double-masked study to ensure that the assessments were not influenced by the knowledge of the specific treatment identity. The patients, the Investigators, the investigational centre staff, the Sponsor, and the clinical monitors were not aware of the treatment assigned to the individual study patients. The external packaging of the study drugs was identical.

***Statistical methods***

Primary and Secondary Efficacy analyses were based on the intent-to-treat (ITT) population – the ITT population being defined as all those who received study medication study medication and had at least one scheduled on-therapy study visit.

The Per Protocol (PP) population included all those who received study medication, had at least one scheduled on-therapy study visit and, in addition and satisfied inclusion/exclusion criteria. This was used for supportive analysis of the primary endpoint.

In accordance with ICH E9 (Statistical Principles for Clinical Trials) results from both data sets have been included in the Clinical Study Report to support the robustness of the efficacy findings.

The primary analysis of both the ITT and PP analysis sets was based on an observed case (OC) analysis.

The statistical model employed, and its associated analysis, was considered robust for random missing data. For the primary efficacy endpoint, a sensitivity analysis using last-observation-carried forward (LOCF) on the primary analysis set (ITT) was performed. The LOCF was used to impute values for dropouts and for missing data for IOP values at all on-therapy visits for the primary efficacy analysis using the ITT data set. If a patient missed an on-therapy visit, the most recently measured on-therapy IOP for the same time of day was used to impute the IOP at the missed visit. Similarly, if a patient is discontinued from the study, the last on-therapy IOP measurement for each time of day was carried forward to replace the IOP measurements for the visit.

Overall, the results of 5 sensitivity analyses consistently supported the results obtained in the primary efficacy analysis that used the observed data. These analyses included a comparison of mean IOP measurements by visit using the treatment received (ITT), a comparison of the mean IOP measurements by visit using the ITT data with LOCF, a comparison of the mean changes in IOP measurements from baseline to each visit using the ITT data with LOCF, an analysis of the

mean IOP with LOCF measurements by visit using a 2-sample t-test procedure (ITT), and an analysis of the change in IOP with LOCF measurements by visit using a 2-sample t-test procedure (ITT). Given this, the results of the study conducted without imputing missing data were considered robust.

No multiplicity adjustment was needed for the primary hypothesis test since all 3 time points for all on-therapy study visits are required to satisfy the equivalence criterion via the intersection-union principle, meaning that in order to demonstrate equivalence, all of the confidence limits must be within ± 1.5 mmHg, the margin of clinical relevance.

In study C-11-34, which tested equivalence as the primary statistical objective, treatment group differences in mean IOP were examined with a pairwise test at each scheduled on therapy study visit and time point. Pairwise t-tests and confidence intervals (CIs) were based on the least squares means derived from a statistical model that accounts for correlated IOP measurements within patient and includes baseline IOP stratum and investigational centre as covariates. Descriptive statistics were summarised for IOP at each on-therapy visit (Week 2, Week 6, and Month 3) and assessment time point (8 am, 10 am and 4 pm). Equivalence was concluded if the 2-sided 95% confidence interval for the difference in IOP (Travoprost 0.003% Solution group minus Travoprost 0.004% BAK group) was within ± 1.5 mmHg at each of the 3 time points (8 am, 10 am and 4 pm) for each on-therapy visit (Week 2, Week 6, and Month 3). In addition, based on historical precedence, it was a requirement in the USA to also demonstrate that the majority of the confidence intervals also lay entirely within ± 1.0 mmHg and this was included as a requirement to establish equivalence for the purpose of US Health Authority (FDA) consideration only.

Descriptive statistics were used to summarise IOP and each of the supportive efficacy variables at each on-therapy visit (Week 2, Week 6, and Month 3) and assessment time point (8 am, 10 am, and 4 pm). Additionally, treatment group differences in the mean IOP change from baseline were examined using a pairwise test at each scheduled on-therapy visit and assessment time point. The pairwise tests were based on the least squares means derived from a statistical model that accounted for correlated IOP measurements within patient where the investigational centre and the 8 AM baseline IOP strata were included in the model.

***Results:***

***Participant flow***

Overall, 864 patients were randomised; 442 to the Travoprost 0.003% Solution group and 422 to Travatan group. The disposition of the patients is shown in Figure 2.

Overall, 24 patients (2.8%) discontinued early from the study, including 10 (0.2%) in the Travoprost 0.003% Solution group and 14 (0.3%) in the Travatan group (table 10.1.5).

The most common reasons for discontinuation were AEs (n=7), followed by inadequate control of IOP (n=6) and patient decision unrelated to an AE (n=6) (table 10.1.5)). At least 96.7% in each group completed the study and the proportion of patients in each group who discontinued early from the study was similar.

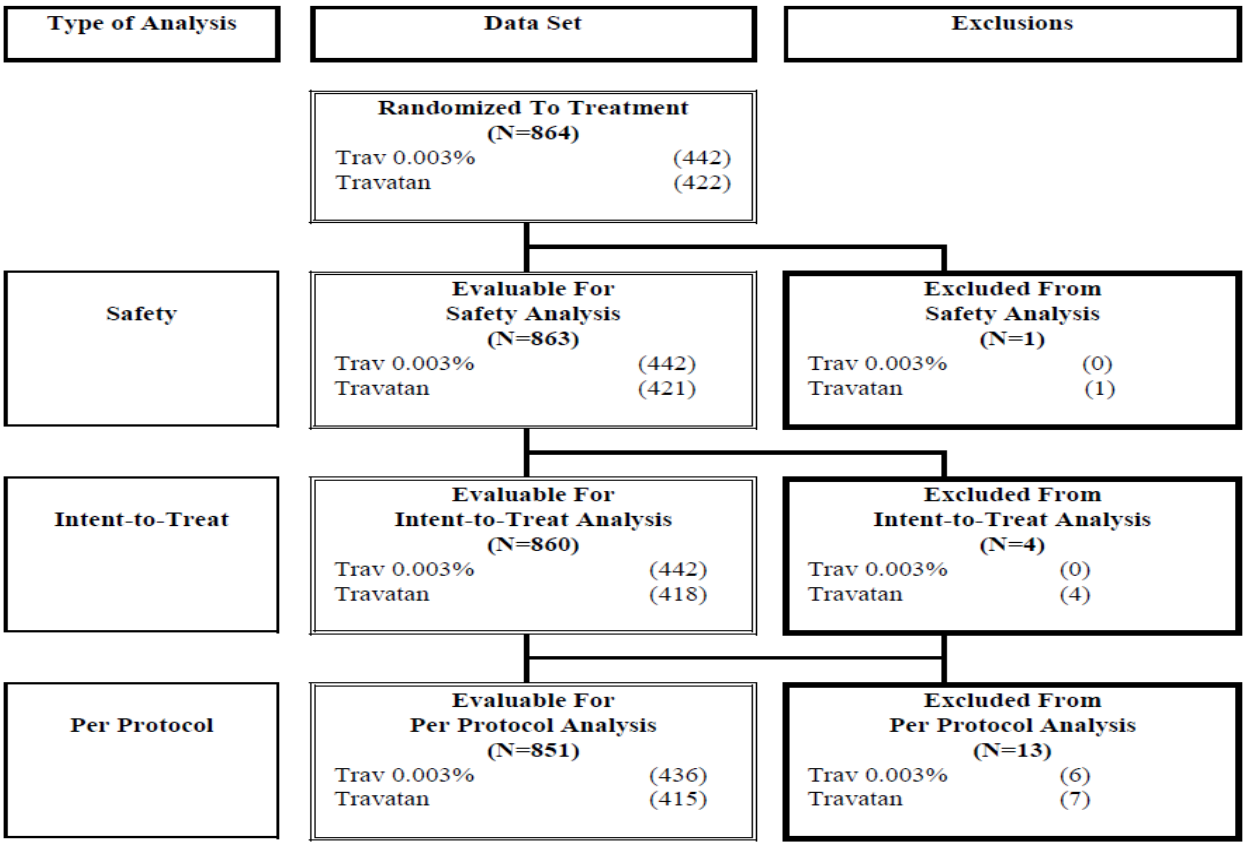
In general, similar percentages of patients in each treatment group discontinued due to an AE, and identical numbers of patients in each treatment group discontinued due to a decision unrelated to an AE. A slightly greater percentage of patients who discontinued due to inadequate control of IOP were in the Travatan group (1.2% vs. 0.2% for Travoprost 0.003%).

**Table 10.1-5:**
**Reasons for Study Discontinuation**
**(All Randomized Patients)**

| | Total (N = 864) | | Trav 0.003% (N = 442) | | Travatan (N = 422) | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| **Total** | **24** | | **10** | | **14** | |
| **Adverse Event** | 7 | (0.8) | 3 | (0.7) | 4 | (0.9) |
| **Lost to Follow-Up** | 3 | (0.3) | 2 | (0.5) | 1 | (0.2) |
| **Patient's Decision Unrelated to an Adverse Event** | 6 | (0.7) | 3 | (0.7) | 3 | (0.7) |
| **Noncompliance** | 1 | (0.1) | 1 | (0.2) | 0 | (0.0) |
| **Inadequate Control of IOP** | 6 | (0.7) | 1 | (0.2) | 5 | (1.2) |
| **Other** | 1 | (0.1) | 0 | (0.0) | 1 | (0.2) |

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK

**Figure 2: Patient Disposition**




Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK

**Conduct of the study**

In 13 patients there were protocol deviations which were sufficient to exclude them from one or more of the analysis sets (Table 6).

**Table 6: Important Protocol Deviations Leading to Patient Exclusion from an Analysis Set**

| Patient Number | Study Drug | Deviation | Excluded Analysis Set |
|---|---|---|---|
| 1354 | Travatan | No on-therapy follow-up data | ITT, PP |
| 1411 | Trav 0.003% | Violation of exclusion criteria | PP |
| 1502 | Trav 0.003% | Violation of exclusion criteria | PP |
| 1808 | Travatan | Violation of exclusion criteria | PP |
| 1955 | Trav 0.003% | Violation of exclusion criteria | PP |
| 2201 | Travatan | Violation of exclusion criteria | PP |
| 2559 | Trav 0.003% | Violation of exclusion criteria | PP |
| 2705 | Trav 0.003% | Violation of exclusion criteria | PP |
| 3201 | Travatan | Violation of exclusion criteria | PP |
| 4229 | Travatan | No on-therapy follow-up data | ITT, PP |
| 4651 | Travatan | No on-therapy follow-up data | ITT, PP |
| 6555 | Travatan | Did not receive study drug | ITT, PP, Safety |
| 7607 | Trav 0.003% | Violation of exclusion criteria | PP |

One patient in the Travatan group did not receive study drug and was therefore excluded from the ITT, PP, and safety analysis sets. An additional 3 patients (again, all on Travatan had no on-therapy follow-up data and were therefore excluded from the ITT and PP analysis sets. Finally, nine other patients (six in the Travoprost 0.003% group and 3 in the Travatan group) violated one or more of the exclusion criteria and were therefore excluded from the PP analysis set. A further 27 patients (11 in the Travoprost 0.003% group and 16 on Travatan) had protocol deviations that resulted in data from one or more individual assessment time points being excluded from the PP analysis set. In all but one case, the deviation was the result of an inadequate time interval between dosing and the IOP measurement or a violation of an exclusion criterion. Two patients (1107 and 7801) were dispensed the wrong study drug at Week 6 and therefore had no data at Month 3 included in the PP analysis.

***Baseline data***

All 60 study centres, with one exception, randomised at least one patient and the enrolled patients were representative of the population that would be treated. No efficacy and safety differences due to ethnicity would be expected with Travoprost 0.003% Solution.

The patient demographics confirmed that the study population was representative of the population that would expect to receive Izba. They are also consistent with the demographics of the population enrolled in the safety and efficacy trials that supported the approval of the 40mcg/ml Travoprost formulations.

***Numbers analysed***

These are shown in Figure 2, above.

## Outcomes and estimation

### Summary of main efficacy results

The ITT analysis set was used to conduct the primary efficacy analysis. The PP analysis set was considered supportive and was used only for the primary efficacy endpoint. The safety analysis set included all patients who received study drug. The primary and supportive efficacy analyses were based on observed cases; missing data were not imputed.

In order to conclude equivalence, the 2-sided 95% CI for the difference in IOP between treatment groups (i.e., the mean IOP in the Travoprost 0.003% Solution group minus the mean IOP in the Travatan group) must have been within ± 1.5 mmHg at each of the 3 assessment time points (8 AM, 10 AM, and 4 PM) for each on-therapy visit (Week 2, Week 6, and Month 3). No multiplicity adjustment was needed for the primary hypothesis test.

A sensitivity analysis for the primary efficacy endpoint was performed in which the last observation carried forward (LOCF) method was used to impute values in the ITT analysis set for dropouts and missing IOP data. In order to support the robustness of the LOCF imputation method for missing data, additional imputation methods were used to impute missing values for dropouts and missing data for both IOP and IOP change from baseline at all on-therapy study visits for the primary efficacy analysis using the ITT analysis set. Lastly, pairwise comparisons for changes in mean IOP from baseline were made at each on-therapy study visit and time point using a 2-sample t-test for both the ITT and PP analysis sets.

A total of 864 patients were randomised to one of the treatment groups. A total of 860 patients were included in the ITT analysis. A total of 851 patients enrolled were included in the PP analysis.

Within the ITT analysis set, the patients were primarily 65 years of age and older (55.8%; overall mean age = 65.2 years), female (59.7%), not Hispanic or Latino (87.8%), and White (72.4%); a substantial percentage of the patients were Black/African American (25.3%). A majority of the patients also had brown eyes (60.3%) and a diagnosis of open-angle glaucoma (69.1%). No clinically meaningful differences were observed between study drug groups in regard to any demographic parameter.

No important differences were noted in mean baseline IOP measurements among the study drug groups (see table below).

**Table 11.2.2-1:**
**Descriptive Statistics for Intraocular Pressure (mmHg) at Baseline**
**(Intent-to-Treat Data)**

| Time Point | | Total | Trav 0.003% | Travatan |
|---|---|---|---|---|
| **8 AM** | **N** | 860 | 442 | 418 |
| | **Mean** | 27.0 | 26.9 | 27.1 |
| | **SD** | 2.70 | 2.54 | 2.86 |
| | **(Min, Max)** | (24, 36) | (24, 36) | (24, 36) |
| **10 AM** | **N** | 860 | 442 | 418 |
| | **Mean** | 25.5 | 25.4 | 25.6 |
| | **SD** | 2.99 | 2.83 | 3.15 |
| | **(Min, Max)** | (21, 36) | (21, 36) | (21, 36) |
| **4 PM** | **N** | 860 | 442 | 418 |
| | **Mean** | 24.7 | 24.6 | 24.8 |
| | **SD** | 3.02 | 2.88 | 3.16 |
| | **(Min, Max)** | (21, 36) | (21, 35) | (21, 36) |

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK
SD = Standard Deviation
Baseline is the average of the two eligibility visits if both values were not missing, otherwise the non-missing value of the two visits was used.

The mean corneal thickness at baseline across study drug groups was 552.4 µm. No meaningful differences in baseline corneal thickness measurements were observed between study drug groups.

Primary Efficacy Results

The IOP-lowering efficacy of Travoprost 0.003% Solution was equivalent to Travatan at all on-therapy study visits (Weeks 2, Week 6, and Month 3) and assessment time points (8 AM, 10 AM, and 4 PM on each visit day).

The least squares mean treatment group differences ranged from -0.3 to 0.0 mmHg with CIs ranging from -0.7 to 0.4 mmHg. Thus, equivalence was met since all 9 of the assessments had CIs that were entirely within the prespecified ± 1.5 mmHg margin. Further, all 9 of the assessments had CIs that were entirely within a ± 1.0 mmHg margin.

**Table 11.4.1.1-1:**
**Comparison of Mean IOP (mmHg) at Week 2, Week 6, and Month 3**
**(Intent-to-Treat Data)**

| | | Trav 0.003% | | Travatan | | | |
|---|---|---|---|---|---|---|---|
| Visit | Time Point | N | Mean (SE) | N | Mean (SE) | Mean Difference[a] | (95% CI) |
| Week 2 | 8 AM | 442 | 19.4 (0.16) | 416 | 19.5 (0.17) | -0.1 | (-0.5, 0.3) |
| | 10 AM | 442 | 18.6 (0.16) | 416 | 18.6 (0.16) | -0.0 | (-0.4, 0.4) |
| | 4 PM | 442 | 18.0 (0.16) | 416 | 18.3 (0.16) | -0.3 | (-0.7, 0.1) |
| Week 6 | 8 AM | 439 | 19.3 (0.16) | 413 | 19.3 (0.17) | -0.0 | (-0.4, 0.4) |
| | 10 AM | 440 | 18.5 (0.16) | 413 | 18.6 (0.17) | -0.1 | (-0.5, 0.3) |
| | 4 PM | 440 | 18.0 (0.16) | 413 | 18.1 (0.17) | -0.2 | (-0.6, 0.2) |
| Month 3 | 8 AM | 432 | 19.2 (0.17) | 408 | 19.3 (0.18) | -0.1 | (-0.5, 0.3) |
| | 10 AM | 432 | 18.3 (0.17) | 408 | 18.6 (0.18) | -0.3 | (-0.7, 0.1) |
| | 4 PM | 431 | 18.0 (0.16) | 408 | 18.0 (0.17) | 0.0 | (-0.4, 0.4) |

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK
SE = Standard Error; CI = Confidence Interval
[a]Estimates based on least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where site and actual 8 AM baseline IOP stratum are in the model.

The overall results at all study visits and assessment time points were similar the PP analysis set.

**Table 14.2-1:**
**Comparison of Mean IOP (mmHg) at Week 2, Week 6, and Month 3**
**(Per Protocol Data)**

| | | Trav 0.003% | | Travatan | | | |
|---|---|---|---|---|---|---|---|
| Visit | Time Point | N | Mean (SE) | N | Mean (SE) | Mean Difference[a] | (95% CI) |
| Week 2 | 8 AM | 435 | 19.4 (0.16) | 409 | 19.5 (0.17) | -0.1 | (-0.5, 0.3) |
| | 10 AM | 435 | 18.6 (0.16) | 409 | 18.6 (0.17) | -0.0 | (-0.4, 0.4) |
| | 4 PM | 435 | 18.0 (0.16) | 409 | 18.3 (0.17) | -0.3 | (-0.7, 0.1) |
| Week 6 | 8 AM | 430 | 19.3 (0.17) | 403 | 19.3 (0.17) | -0.0 | (-0.4, 0.4) |
| | 10 AM | 430 | 18.5 (0.16) | 403 | 18.6 (0.17) | -0.2 | (-0.6, 0.3) |
| | 4 PM | 431 | 17.9 (0.16) | 403 | 18.1 (0.17) | -0.2 | (-0.6, 0.2) |
| Month 3 | 8 AM | 420 | 19.1 (0.17) | 396 | 19.3 (0.18) | -0.2 | (-0.6, 0.3) |
| | 10 AM | 420 | 18.3 (0.17) | 396 | 18.6 (0.18) | -0.3 | (-0.8, 0.1) |
| | 4 PM | 419 | 18.0 (0.16) | 396 | 18.0 (0.17) | -0.0 | (-0.4, 0.4) |

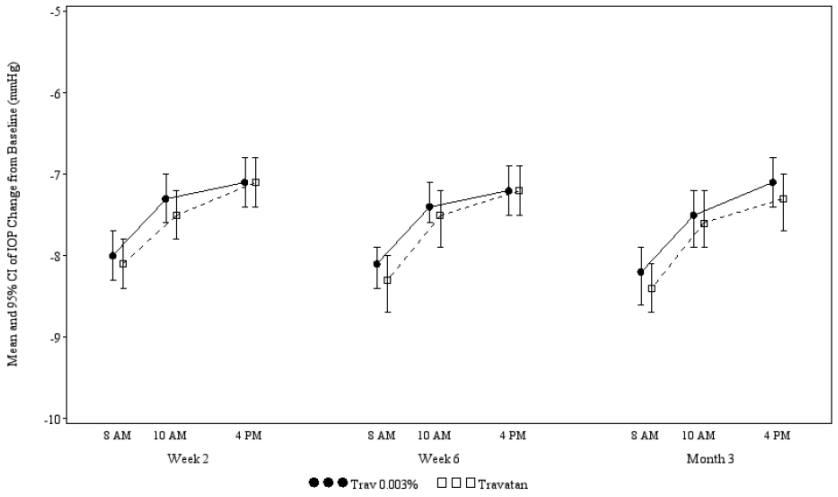
Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK
SE = Standard Error; CI = Confidence Interval
[a]Estimates based on least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where site and actual 8 AM baseline IOP stratum are in the model.

Secondary Efficacy Results

The changes and percent changes in IOP from baseline to each study visit and assessment time point showed no marked differences between treatment groups.

The mean reductions in IOP within the Travoprost 0.003% Solution group ranged from 7.1 to 8.2 mmHg; the mean reductions in IOP within the Travatan group ranged from 7.1 to 8.4 mmHg.

**Figure 11.4.1.2-2:**
**Means and 95% Confidence Intervals for IOP Changes from Baseline (mmHg) by Visit**
**(Intent-to-Treat Data)**




The percent reductions in IOP from baseline to each study visit and assessment time point ranged from 28.4% to 30.7%

**Table 11.4.1.2-4:**
**Descriptive Statistics for IOP Percent Change from Baseline (mmHg) by Visit**
**(Intent-to-Treat Data)**

| | | Trav 0.003% | | | Travatan | | |
|---|---|---|---|---|---|---|---|
| **Visit** | | **8 AM** | **10 AM** | **4 PM** | **8 AM** | **10 AM** | **4 PM** |
| **Week 2** | **N** | 442 | 442 | 442 | 416 | 416 | 416 |
| | **Mean** | -29.7 | -28.4 | -28.7 | -29.9 | -29.3 | -28.5 |
| | **SD** | 10.67 | 10.97 | 11.43 | 11.33 | 11.44 | 11.55 |
| | **(Min, Max)** | (-58, 0) | (-61, 11) | (-59, 9) | (-60, 4) | (-63, 9) | (-59, 5) |
| | **95% CI** | (-30.7, -28.7) | (-29.4, -27.4) | (-29.7, -27.6) | (-31.0, -28.8) | (-30.4, -28.2) | (-29.6, -27.4) |
| **Week 6** | **N** | 439 | 440 | 440 | 413 | 413 | 413 |
| | **Mean** | -30.3 | -28.9 | -28.8 | -30.8 | -29.4 | -29.1 |
| | **SD** | 10.78 | 10.89 | 11.35 | 11.36 | 11.36 | 11.11 |
| | **(Min, Max)** | (-61, 14) | (-62, 8) | (-63, 4) | (-65, 8) | (-59, 14) | (-57, 8) |
| | **95% CI** | (-31.3, -29.3) | (-30.0, -27.9) | (-29.9, -27.7) | (-31.9, -29.7) | (-30.5, -28.3) | (-30.2, -28.0) |
| **Month 3** | **N** | 432 | 432 | 431 | 408 | 408 | 408 |
| | **Mean** | -30.7 | -29.5 | -28.5 | -31.0 | -29.5 | -29.4 |
| | **SD** | 11.29 | 11.44 | 11.48 | 10.93 | 11.50 | 11.37 |
| | **(Min, Max)** | (-61, 30) | (-59, 8) | (-63, 9) | (-60, 11) | (-64, 25) | (-64, 17) |
| | **95% CI** | (-31.7, -29.6) | (-30.6, -28.5) | (-29.6, -27.4) | (-32.1, -30.0) | (-30.6, -28.4) | (-30.5, -28.3) |

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
Travatan = Travoprost 40 µg/mL eye drops, solution preserved with BAK
SD = Standard Deviation; CI = Confidence Interval

Approximately 33% to 55% of the patients had an IOP measurement below 18 mmHg during the study. At every study visit and assessment time point, at least 43.9% of the patients in the Travoprost 0.003% Solution group and 44.2% of the patients in the Travatan group had a reduction in IOP of at least 30% relative to baseline. No marked differences were noted between treatment groups at any specific assessment.

**Summary of main study**

The following table summarises the efficacy results from the main studies supporting this MA application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see relevant sections). Only results on primary endpoint are presented. Relevant results of secondary parameters are included in other sections of the report.

**Tabular Summary of Efficacy for trial C-11-034**

<table>
<tr><td colspan="4">Title: A Multicenter, Double-Masked Study of the Safety and Efficacy of Travoprost Ophthalmic Solution, 0.003% Compared to Travatan in Patients with Open-Angle Glaucoma or Ocular Hypertension</td></tr>
<tr><td>Study identifier</td><td colspan="3">C-11-34</td></tr>
<tr><td rowspan="4">Design</td><td colspan="3">Multicenter, double-masked, randomized, active-controlled, 2-arm, parallel-group, equivalence study designed to evaluate the safety and efficacy of Travoprost 0.003% Solution relative to Travatan in adult patients with open-angle glaucoma or ocular hypertension.</td></tr>
<tr><td colspan="2">Duration of main phase:</td><td>3 months</td></tr>
<tr><td colspan="2">Duration of Run-in phase:</td><td>not applicable</td></tr>
<tr><td colspan="2">Duration of Extension phase:</td><td>not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Equivalence between Travoprost 0.003% Solution and Travoprost 0.004% BAK (Travatan®)</td></tr>
<tr><td rowspan="3">Treatments groups</td><td colspan="2">Travoprost 0.003% Solution</td><td>Dosing regimen: 1 drop in the treated eye(s) once daily at 8 PM<br>Dosing duration: 3 months<br>Number randomized: 442 patients</td></tr>
<tr><td colspan="2">Travoprost 0.004% BAK</td><td rowspan="2">Dosing regimen: 1 drop in the treated eye(s) once daily at 8 PM<br>Dosing duration: 3 months<br>Number randomized: 422 patients</td></tr>
<tr><td rowspan="2">Endpoints and definitions</td><td>Primary endpoint</td><td></td><td rowspan="2">IOP at Week 2, Week 6, and Month 3 for each assessment time point (8 AM, 10 AM, and 4 PM).</td></tr>
</table>

| | | | |
|---|---|---|---|
| | Secondary endpoint: Efficacy | | • Change from baseline in IOP and percent change from baseline in IOP at each visit (Week 2, Week 6, and Month 3) and assessment time point (8 AM, 10 AM, and 4 PM).<br>• Percentage of patients who achieved a target IOP level < 18 mmHg at each visit (Week 2, Week 6, and Month 3) and assessment time point (8 AM, 10 AM, and 4 PM).<br>• Percentage of patients who achieved IOP-lowering of at least 30% from baseline at each visit (Week 2, Week 6, and Month 3) and assessment time point (8 AM, 10 AM, and 4 PM). |
| Database lock | 23 August 2012 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat (all randomized subjects who received study drug and completed at least one scheduled on-therapy study visit)<br><br>Time points: 3 assessment time points (8 AM, 10 AM, and 4 PM) for each on-therapy study visit (Week 2, Week 6, and Month 3). | | |
| Descriptive statistics and estimate variability | Mean IOP (mmHg) | | |
| | Treatment group | Travoprost 0.003% Solution<br><br>Mean (SE) (a) | Travoprost 0.004% BAK (TRAVATAN®)<br>Mean (SE) (a) |
| | Number of subjects | 442 | 418 |
| | **W2** 8 AM | 19.4 (0.16) | 19.5 (0.17) |
| | 10 AM | 18.6 (0.16) | 18.6 (0.16) |
| | 4PM | 18.0 (0.16) | 18.3 (0.16) |
| | **W6** 8 AM | 19.3 (0.16) | 19.3 (0.17) |
| | 10 AM | 18.5 (0.16) | 18.6 (0.17) |
| | 4 PM | 18.0 (0.16) | 18.1 (0.17) |

| | | | |
|---|---|---|---|
| | **M3** 8 AM | 19.2 (0.17) | 19.3 (0.18) |
| | 10 AM | 18.3 (0.17) | 18.6 (0.18) |
| | 4 PM | 18.0 (0.16) | 18.0 (0.17) |
| Effect estimate per comparison | Mean difference IOP (mmHg) between Travoprost 0.003% Solution and Travoprost 0.004% BAK (TRAVATAN®) | | |
| | Visit/Time point | Mean difference IOP (mmHg) (a) | 95% (2-sided CI) |
| | **W2** 8 AM | -0.1 | (-0.5, 0.3) |
| | 10 AM | -0.0 | (-0.4, 0.4) |
| | 4PM | -0.3 | (-0.7, 0.1) |
| | **W6** 8 AM | -0.0 | (-0.4, 0.4) |
| | 10 AM | -0.1 | (-0.5, 0.3) |
| | 4 PM | -0.2 | (-0.6, 0.2) |
| | **M3** 8 AM | -0.1 | (-0.5, 0.3) |
| | 10 AM | -0.3 | (-0.7, 0.1) |
| | 4 PM | 0.0 | (-0.4, 0.4) |
| Note | (a) Estimates based on least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where site and actual 8 AM baseline IOP stratum are in the model. | | |

## 2.5.2. Discussion on clinical efficacy

One single clinical trial was submitted to support the efficacy and safety of the 0.003% strength for Travoprost. The main objective of the Study C-11-034 was to establish the comparability (non-inferiority) between Travoprost 0.003% PQ (the new formulation) and Travoprost 0.004% BAK (the original formulation). The travoprost 0.004% formulation was modified in 2010 in order to replace the preservative used benzalkonium chloride (BAK) by polyquaternium-1 (POLYQUAD, PQ) so that the comparator used in this trial did not exactly correspond to that available on the market at the time of submission of this MAA.

No specific dose selection studies were conducted in order to find out if there could be a lower, efficacious dose. The rationale for the 30 μg/mL choice was based on the available data of studies previously conducted to support the marketing authorisation of the original formulation (Travatan BAK). Dose-response studies revealed that doses equal or higher than 0.002% reached significant (and quantitatively similar) IOP reductions. The greatest IOP lowering efficacy was shown by Travoprost 0.004%. This effect was confirmed during Phase III. Travoprost 0.003% concentration was not specifically tested in those trials. The CHMP obtained satisfactory clarifications from the applicant over the justification of the dose chosen. However, in order to

better address this topic, the MAH is encouraged to further investigate the efficacy of a lower concentration product, since studies with the 30 µg/ml dose, PD and historical clinical data indicate that even lower doses may be also applied.

**Design and conduct of clinical studies**

Study C-11-034 was performed with the aim to demonstrate the non-inferior IOP lowering efficacy of a reduced concentration formulation of travoprost (polyquad preserved Travoprost 0.003) in patients with open-angle glaucoma or ocular hypertension. The non-inferiority was determined versus Travatan BAK (benzalkonium preserved Travoprost 0.004%) instead of the currently available polyquad preserved Travoprost 0.004% formulation. The Applicant has justified the choice on the fact that the original dossier was performed with the BAK formulation. In addition, the non-inferiority between Travoprost 0.004% BAK and PQ formulations was demonstrated. However, in order to provide robustness to the comparison the inclusion of the currently available formulation (even a third arm as internal control) would have been of help.

In this new formulation the amount of travoprost (30 µg/mL) has been reduced of one fourth from the original concentration (40 µg/mL). This precise concentration had not been previously tested, although doses between 20 µg and 60 µg/mL showed some efficacy. Whereas the safety profile of the product improved with the replacement of benzalkonium preservative (mainly those adverse effect due to corneal irritation, such as itching and dryness), topical prostaglandins are associated with a number of well-known ocular side effects (hyperaemia, eye irritation, increase in the number and length of eyelashes, changes in the iris and lash pigmentation). Therefore, the key issue was to establish if the proposed reduction in concentration of travoprost had a relevant benefit on the safety of the product without having impact on the IOP lowering effect.

Study C-11-34 is a multicentre, double-masked, randomized, active controlled parallel group study comparing the efficacy of Travoprost 0.004% BAK and Travoprost 0.003% PQ in patients with open-angle glaucoma or ocular hypertension requiring IOP-lowering therapy. The global design of the clinical study (including the selection criteria of the patients, the duration of the study, the choice of endpoints) is in general acceptable and in agreement with other similar trials in the field.

The primary efficacy endpoint is the IOP achieved at Week 2, Week 6 and Month 3 for each assessment time point (8 AM, 10 AM, 4 PM). Beyond absolute IOP levels (primary endpoint), the efficacy measured in terms of IOP changes from baseline (absolute and percent differences) and responder rates (patients achieving IOP < 18 mmHg, patients achieving IOP-lowering ≥30% from baseline) measured as secondary outcomes seem to be of special relevance.

The non-inferiority is to be shown at all three time-points (8 AM, 10 AM, 4 PM) at every follow-up visit (week 2, week 6, month 3), for a total of 9 successful non-inferiority tests. The non-inferiority margin of 1.5 mmHg has been used in other similar trials in the past (included the Study C-08-40, where Travoprost 0.004% BAK and Travoprost 0.004% PQ were compared). This is considered appropriate. Standard time points for IOP measurements (where the time the highest IOP and the maximal IOP lowering effect are included) have been selected.

The main proof of non-inferiority has been performed on the intent-to-treat analysis set. Whereas analyses on the full analysis set (i.e. ITT) have generally been considered not

conservative for non-inferiority studies ('ICH Topic E9 - Statistical Principles for Clinical Trials' (CPMP/ICH/363/96), it should be noted that it also has been specified that both analyses have equal importance and should lead to similar conclusions ('Points to Consider on Switching between Superiority and Non-Inferiority' (CPMP/EWP/482/99). In this sense, although the Per Protocol (PP) set would have been the preferred population for a non-inferiority analysis, disparities between ITT and PP analysis set would not be expected in order to demonstrate the non-inferiority between both treatments and provide robustness to the results.

**Efficacy data and additional analyses**

A total of 864 patients (442 patients in Travoprost 0.003% and 422 in Travoprost 0.004%) were randomised. A total of 860 patients (442 in Travoprost 0.003% and 418 in Travoprost 0.004%) were evaluable for ITT analysis and 851 patients (436/415) were evaluable for PP analysis.

More than 97% of patients completed the treatment period. A total of 24 patients, 14 (3.3%) on Travoprost 0.004% BAK versus 10 patients (2.3%) on Travoprost 0.003% PQ discontinued the study. Lack of control of IOP was reported more frequently in Travoprost 0.004% BAK than in Travoprost 0.003% PQ group (5 vs 1), what was in principle unexpected. No relevant differences between groups were observed with respect to other reasons.

Overall, treatment groups were well balanced with respect to demographic characteristics. As expected, mean age was 65.2 years ranging from 21 to 92 years old, which represents the broad spectrum of the target population. In fact, a high proportion of elderly patients (≈ 56%) were included.

From these data equivalence was shown since all nine assessments conducted exhibited CIs that were entirely within the pre-specified ± 1.5 mmHg margin (actually falling within tighter CIs of a ± 1.0 mmHg margin). Mean IOP reductions from baseline ranged from 7.1 to 8.2 mmHg for Travoprost 0.003% Solution and from 7.1 to 8.4 mmHg for Travoprost 0.004% BAK, corresponding to IOP reductions of 28.7% to 30.7%, and 28.5% to 31.0%, respectively. The magnitudes of IOP reductions are clinically relevant and consistent with those observed with prostaglandin analogues including Travoprost 0.004% BAK as shown in other reported studies. Numerically, a minimal better trend was measured for Travoprost 0.003% PQ group.

The non-inferiority primary analysis was performed on the ITT analysis set, the PP analysis set being considered supportive. Whereas this hierarchy may be object of discussion (see comment above), no differences were observed between both analysis sets.

Minimal differences between groups were also observed when changes in IOP with respect to baseline were compared. Results in PP analysis set were consistent. The 95% CI of the difference between both formulations are within 1 mmHg in all time points. Patients experienced about 30% of reduction of the IOP with both formulations, and this response was numerically similar in the two groups. A greater variability was observed between the groups of treatment and the analysis population sets when the efficacy was measured in terms of responder rates. In any case, no relevant differences were shown.

No long-term studies have been conducted with the new Travoprost 0.003% formulation, but long-term studies (up to 5 years) have been conducted with the currently licensed Travoprost 0.004% BAK and these studies have demonstrated the maintenance of the effect without

development of tolerance. The treatment duration in C-11-034 was 3 months and, based on published literature, this was considered adequate to demonstrate IOP-lowering efficacy of glaucoma medications.

### 2.5.3. Conclusions on clinical efficacy

Non-inferiority of Travoprost 0.003% PQ with respect to Travoprost 0.004% BAK in the treatment of patients with ocular hypertension or open-angle glaucoma was shown in study C-11-034. Although the comparator used in this trial had a different preservative to that currently available in the market (Travoprost 0.004% PQ), the equivalence between the two 0.004% formulations was already proven and, therefore, the indirect evidence was considered sufficient by the CHMP.

Adequate wording is included in the relevant sections of the SmPC and PL that reflect the above assessment.

As a result of the Marketing Authorisation for Izba, two different strengths (one with the original concentration, one with the reduced one) will become available. The two strengths have shown equivalent IOP lowering efficacy and an improved safety profile has been observed for Izba. Upon request of the CHMP, detailed information on the marketing plans for the two strengths (such as approximate time of co-existence of both presentations, any steps proposed to address the potential impact of strength confusion and Travatan withdrawal date) was provided by the Applicant. The MAH informed the CHMP that the co-existence of the two presentations on the market is expected to be approximately 3 years. Activities intended to minimise the risk of confusion by the prescribers and patients appeared advisable. In particular, prescribers could be made aware of the marketing plans to prevent potential confusion between presentations, and should be informed on how to handle the transition from Travatan to Izba.

## *2.6. Clinical safety*

The safety analysis of Travoprost 0.003% solution is based upon the results obtained from the following sources of data:

- 3-month pivotal Phase 3 safety and efficacy study (C-11-034), designed to demonstrate the equivalence of Travoprost 0.003% Solution to Travoprost 0.004% BAK, both dosed once-daily in the evening in patients with open-angle glaucoma or ocular hypertension.

- A comparison of safety data between Travoprost 0.003% Solution (C-11-034 study) and historical safety data from confirmatory clinical trials involved in the development of Travoprost 0.004% BAK (C-97-79, C-97-72 and C-97-71), Travoprost 0.004% SofZia (C-04-17), and Travoprost 0.004% PQ (C-08-40).

Overall, the approach established for the safety analysis is considered acceptable. However, a direct comparison between Travoprost 0.003% and Tavoprost 0.004% using POLIQUAD as preservative in both formulations would have been preferable. This would have deleted any interference in the safety results derived from the different preservatives. On the other hand, some indirect comparisons between Travoprost 0.003% PQ (C-11-034) and historical data of

Tavoprost 0.004% PQ (C-08-40) have been provided. This was considered acceptable as it allows obtaining estimated conclusions regarding the overall safety profile of Travoprost 0.003%.

Only ocular parameters have been measured. However, given that lower systemic exposure is expected when travoprost is topically administered and considering that there is a large amount of data about the safety profile of travoprost 0.004% from clinical studies and post marketing data, the measurements performed are considered acceptable.

**Patient exposure**

On the whole, 442 patients were exposed to one drop of travoprost 0.003% solution in C-11-034 clinical study.

The demographic characteristics of patients include different age groups (56% of patients ≥65 years), patients with a diagnosis of open-angle glaucoma or ocular hypertension, races predisposed to the disease such as Black or African American and baseline IOP ≥ 24 mmHg. In general, the studied population is considered representative of the population that is expected to receive Travoprost 0.003% solution. In addition, they have similar characteristics to the population included in the historical confirmatory studies involving Travoprost 0.004% (Travoprost 0.004% BAK (C-97-79, C-97-72 and C-97-71), Travoprost 0.004% SofZia (C-04-17), and Travoprost 0.004% PQ (C-08-40)).
In general, the safety population included in the main study (C-11-034) is considered appropriate for the overall safety analysis. The safety data collected from historical confirmatory clinical trials are considered supportive data.

Duration of exposure is in general higher than 87 days. The majority of patients (73% in travoprost 0,003% group vs 72% in travoprost 0,004% group) were exposed during 3 months approximately.

Some adverse events already known for topical PGAs generally occur after several months to years of dosing (e.g. periocular skin hyperpigmentation or discolouration, iris hyperpigmentation, and changes in eyelash characteristics). Given that these events are considered identified risks in the RMP and there is a considerable amount of data from long-term clinical studies and post-marketing surveillance with the already approved travoprost formulations, the duration of exposure is considered acceptable.

**Table 2.7.4.1–2 Duration (Days) of Once Daily Exposure to Study Medication - C-11-034**

| | Trav 0.003% (N = 442) | | TRAVATAN (N = 421) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| **1-15 Days** | 0 | (0.0) | 5 | (1.2) |
| **16-45 Days** | 7 | (1.6) | 4 | (1.0) |
| **46-87 Days** | 113 | (25.6) | 111 | (26.4) |
| **>87 Days** | 322 | (72.9) | 301 | (71.5) |

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with Polyquad
TRAVATAN = Travoprost 40 µg/mL eye drops, solution preserved with BAK

**Adverse events**

The overall safety profile might be similar from a qualitative point of view as both treatment groups contain the same active substance (travoprost). However, from a quantitative point of view some differences would be expected as travoprost strength has been reduced 25%. In addition, preservatives of both treatment groups are different (POLYQUAD vs Benzalkonium chloride) and therefore the occurrence of AEs could be either due to the active substance or to the preservative.

As mentioned above, a direct comparison using the same preservative would have been the preferable approach. However, as no new AEs and no significant difference between treatment groups have been found during study C-11-034, an indirect comparison Travoprost 0.003% PQ vs Travoprost 0.004% PQ could be considered suitable to compare the two safety profiles.

As expected, the majority of AEs reported for either treatment group during clinical trial C-11-034 were local ocular effects and they were in general consistent with the known safety profile of the use of travoprost and topical ocular PGAs.

The most common AE reported during the C-11-034 study was hyperaemia of the eye (ocular or conjunctival). A lower incidence of hyperaemia in Travoprost 0.003% group (12.7%) was observed in comparison to Travoprost 0.004% BAK (15.2%). When comparing each type of hyperaemia in both groups, a lower incidence was also seen with the lower dose of travoprost (ocular: 7.0% vs 8.1% and conjunctival: 5.7% vs 7.1%).

Furthermore, concerning adverse drug reactions (ADRs) to study drug, the following data also showed a less incidence of hyperaemia with travoprost 0.003% in comparison to travoprost 0.004% BAK at Month 3:

- 11.8% vs 14.5% (total ADRs for hyperaemia)
- 6.1% vs 7.6% (ocular hyperaemia)
- 5.7% vs 6.9% (conjunctival hyperaemia)

The 90% of hyperaemias were mild in severity. In relation to discontinuations due to hyperaemia, one patient in Travoprost 0.003% group discontinued compared to 2 patients in Travoprost 0.004% BAK group.

Regarding local tolerance to the study medication (defined as the MedDRA preferred terms of eye irritation, eye pain, eye pruritus, eyelids pruritus, foreign body sensation in eyes and ocular or conjunctival hyperaemia), similar observations were reported between groups.

**Table 2.7.4.2–2 Summary of Treatment-Emergent Adverse Events**

| Adverse Event Category | Trav 0.003% N = 442 | | TRAVATAN N = 421 | |
|---|---|---|---|---|
| | N | % | N | % |
| **Deaths** | **0** | **0.0** | **0** | **0.0** |
| **Patients experiencing nonfatal SAEs** | **5** | **1.1** | **7** | **1.7** |
| Treatment-related | 0 | 0.0 | 0 | 0.0 |
| Not related to treatment | 5 | 1.1 | 7 | 1.7 |
| **Patients discontinued due to an AE** | **3** | **0.7** | **4** | **1.0** |
| Discontinued due to nonfatal serious AE | 0 | 0.0 | 0 | 0.0 |
| Discontinued due to nonserious AE | 3 | 0.7 | 4 | 1.0 |
| Treatment-related | 2 | 0.5 | 3 | 0.7 |
| Not related to treatment | 1 | 0.2 | 1 | 0.2 |
| **Patients with at least 1 treatment-emergent AE (related and not related combined)** | **134** | **30.3** | **136** | **32.3** |
| Most frequent treatment-emergent AEs (≥ 5%) | | | | |
| Ocular hyperaemia | 31 | 7.0 | 34 | 8.1 |
| Conjunctival hyperaemia | 25 | 5.7 | 30 | 7.1 |
| **Patients with at least 1 treatment-emergent AE related to treatment (adverse drug reaction)** | **79** | **17.9** | **80** | **19.0** |
| Most frequent ADR (incidence of 1% or greater) | | | | |
| Ocular hyperaemia | 27 | 6.1 | 32 | 7.6 |
| Conjunctival hyperaemia | 25 | 5.7 | 29 | 6.9 |
| Total ADRs for Hyperemia of the Eye (ocular and conjunctival combined) | 52 | 11.8 | 61 | 14.5 |
| Eye pruritus | 12 | 2.7 | 8 | 1.9 |
| Eye irritation | 9 | 2.0 | 5 | 1.2 |
| Dry eye | 6 | 1.4 | 5 | 1.2 |
| Photophobia | 2 | 0.5 | 4 | 1.0 |

Trav 0.003% = Travoprost 0.003% Solution
TRAVATAN = Travoprost 0.004% BAK

**Table 2.7.4.2–4 Overall Frequency and Incidence of Adverse Events Classified as Ocular Intolerance – C-11-034**

| | Trav 0.003% (N=442) | | | | | | TRAVATAN (N=421) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | R | | NR | | Total | | R | | NR | | Total | |
| **Coded Adverse Event** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Eye disorders** | | | | | | | | | | | | |
| Ocular hyperaemia | 27 | 6.1 | 6 | 1.4 | 31 | 7.0 | 32 | 7.6 | 3 | 0.7 | 34 | 8.1 |
| Conjunctival hyperaemia | 25 | 5.7 | | | 25 | 5.7 | 29 | 6.9 | 3 | 0.7 | 30 | 7.1 |
| Eye pruritus | 12 | 2.7 | 3 | 0.7 | 15 | 3.4 | 8 | 1.9 | 2 | 0.5 | 10 | 2.4 |
| Eye irritation | 9 | 2.0 | 1 | 0.2 | 10 | 2.3 | 5 | 1.2 | 1 | 0.2 | 6 | 1.4 |
| Eye pain | 2 | 0.5 | 1 | 0.2 | 3 | 0.7 | 2 | 0.5 | 2 | 0.5 | 4 | 1.0 |
| Foreign body sensation in eyes | 2 | 0.5 | 2 | 0.5 | 4 | 0.9 | 1 | 0.2 | | | 1 | 0.2 |
| Eyelids pruritus | | | 1 | 0.2 | 1 | 0.2 | 1 | 0.2 | | | 1 | 0.2 |

Coded adverse event = MedDRA Preferred Term (version 14.0) presented by System Organ Class.
Ocular intolerance consists of the observed preferred terms conjunctival hyperaemia, eye irritation, eye pain, eye pruritus, eyelids pruritus, foreign body sensation in eyes and ocular hyperaemia

Only one patient reported dark circles under the eye (classified under the SOC Eye disorders according to MeDRA). In addition, it is of note that no periocular skin discolouration, iris hyperpigmentation and changes in eyelash characteristics were reported. Given that these effects are related to the topical use of PGAs and likely related to the prolonged use of travoprost, the potential occurrence of these AEs over time cannot be ruled out. As a consequence, these events are already classified in the RMP as identified risks.

Regarding non-ocular adverse events, one case of pruritus and one case of rash were reported as related to Travatan 0.003%.

On the other hand, it is of note that in general no new AE different from the already known safety profile for travoprost was reported.

On the whole, safety data submitted for study C-11-034 seem to be reassuring as they are consistent with PGAs effects and with the already known safety profile for travoprost. These data are considered the expected results when a lower dose of travoprost is administered into the eye. In general, lower exposure to travoprost resulted in a slightly lower incidence of AEs reported in patients dosing with Travoprost 0.003% solution in relation to Travoprost 0.004% BAK.

Regarding ADRs for hyperaemia when comparing both formulations including the same preservative POLYQUAD (travoprost 0.003% PQ vs historical safety data of travoprost 0.004% PQ), the following conclusions are considered relevant:

- These comparative data will provide reliable data to guarantee a conclusion concerning the possible improved safety profile of travoprost 0.003%.
- Lower exposure to travoprost causes less incidence of hyperaemia:
  - 11.8% in Travoprost 0.003% PQ
  - 15.1% in Travoprost 0.004% PQ
  - 38.8% in Travoprost 0.004% BAK
- Benzalkonium chloride seems to have a negative impact in the incidence of hyperaemia as historical data for Travoprost 0.004% BAK revealed an incidence of 38.8% vs 11.8% for Travoprost 0.003% PQ and 15.1% for Travoprost 0.004% PQ.
- No unexpected safety issues were identified when comparing Travoprost 0.003% Solution and historical AEs for Travoprost 0.004% (preserved with BAK, sofZia or PQ).

**Table 2.7.4.2–6** **Overall Frequency and Incidence of Adverse Drug Reactions for Hyperemia of the Eye - Travoprost 0.003% Solution compared to Travoprost 0.004% (PQ, Z, and BAK)**

| | Travoprost 0.003% (N=442) (C-11-034[a]) | | Travoprost 0.004% PQ (N=185) (C-08-40[a]) | | Travoprost 0.004% sofZia (N=344) (C-04-17) | | Travoprost 0.004% BAK (N= 598) C-97-71, C-97-72, C-97-79) | |
|---|---|---|---|---|---|---|---|---|
| **Coded Adverse Drug Reaction** | **Total** | | **Total** | | **Total** | | **Total** | |
| | **N** | **%** | **N** | **%** | **N** | **%** | **N** | **%** |
| **Eye disorders** | | | | | | | | |
| Ocular hyperaemia | 27 | 6.1 | 21 | 11.4 | 21 | 6.1 | 222 | 37.1 |
| Conjunctival hyperaemia | 25 | 5.7 | 7 | 3.8 | - | - | 10 | 1.7 |
| Hyperemia of the eye | 52 | 11.8 | 28 | 15.1 | 21 | 6.1 | 232 | 38.8 |

Coded adverse event = MedDRA Preferred Term (version 14.0) presented by System Organ Class.
Adverse Drug Reactions = Treatment-related adverse events
Data presented in the table is a subset of Table Table 2.7.4.7–1, Table 2.7.4.7–5, and Table 2.7.4.7–7.
[a]No patients were reported to have both ocular and conjunctival hyperaemia

Regarding ADR for ocular intolerance to the study medication, it is observed that the local tolerance is generally improved with lower exposure to travoprost in comparison to historical data (Travoprost 0.004% PQ, Sofzia or BAK). It is noteworthy that some different Preferred Terms (PTs) have been included for the assessment of the local tolerance (i.e. ocular discomfort in historical confirmatory studies and ocular hyperaemia/conjunctival hyperaemia in study C-11-034). However, globally, all the results extracted from the seven PTs that cover the term 'local tolerance' reveal a lower incidence of AEs with Travoprost 0.003% PQ compared to historical data of Travoprost 0.004% (PQ, BAK and Sofzia).

No unexpected ADRs different from the AEs already known for travoprost 0.004% were reported.

**Table 2.7.4.2–5 Overall Frequency and Incidence of Adverse Drug Reactions Classified as Ocular Intolerance – Travoprost 0.003% Solution compared to Travoprost 0.004% (PQ, sofZia, and BAK)**

| | Trav 0.003% (N=442) | | Travoprost 0.004% PQ (N=185) | | Travoprost 0.004% sofZia (N=344) | | Travoprost 0.004% BAK* (N=532) | |
|---|---|---|---|---|---|---|---|---|
| | Total | | Total | | Total | | Total | |
| **Coded Adverse Drug Reaction** | | | | | | | | |
| **Eye disorders** | | | | | | | | |
| Eye pruritus | 12 | 2.7 | 7 | 3.8 | 18 | 5.2 | 17 | 3.2 |
| Eye irritation | 9 | 2.0 | 6 | 3.2 | 12 | 3.5 | 13 | 2.4 |
| Eye pain | 2 | 0.5 | 3 | 1.6 | 6 | 1.7 | 7 | 1.3 |
| Foreign body sensation in eyes | 2 | 0.5 | 5 | 2.7 | 9 | 2.6 | 8 | 1.5 |
| Eyelids pruritus | - | - | - | - | 3 | 0.9 | - | - |
| Ocular discomfort | - | - | - | - | - | - | 2 | 0.4 |

Coded adverse event = MedDRA Preferred Term (version 14.0) presented by System Organ Class.
Adverse Drug Reactions = Treatment-related adverse events
Ocular intolerance consists of the observed preferred terms ocular discomfort, eye irritation, eye pain, eye pruritus, eyelids pruritus, and foreign body sensation in eyes
*Data for Travoprost 0.004% BAK are from clinical studies C-04-17 and C-08-40 combined.
Data presented in the table is a subset of Table 2.7.4.7–1 and Table 2.7.4.7–5.

### Serious adverse event / deaths / other significant events

No patient deaths and no SAE related to study drug were reported in clinical trial C-11-034.

### Laboratory findings

Data related to changes in ocular hyperaemia and ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, lens, aqueous cells/flare) were reported.

In general, the safety profile of the submitted medicinal product is slightly improved, in terms of hyperaemia, compared to the already approved travoprost.

**Table 2.7.4.4–3 Descriptive Statistics for Hyperemia Score by Visit – C-11-034**

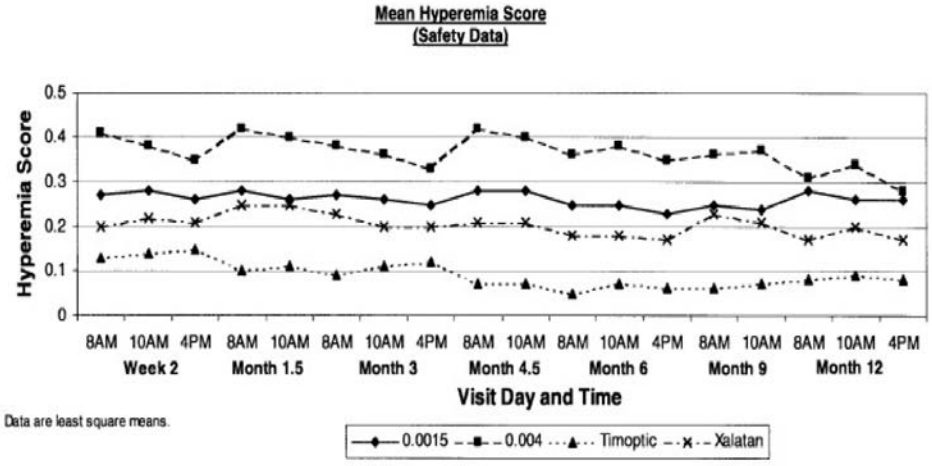
| | | Trav 0.003% | | | TRAVATAN | | |
|---|---|---|---|---|---|---|---|
| **Visit** | | **8 AM** | **10 AM** | **4 PM** | **8 AM** | **10 AM** | **4 PM** |
| **Baseline** [a] | **N** | 442 | 442 | 442 | 421 | 421 | 421 |
| | **Mean** | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| | **SD** | 0.39 | 0.36 | 0.37 | 0.38 | 0.35 | 0.38 |
| | **(Min, Max)** | (0, 2) | (0, 2) | (0, 2) | (0, 3) | (0, 3) | (0, 3) |
| **Week 2** | **N** | 442 | 442 | 442 | 416 | 416 | 416 |
| | **Mean** | 0.4 | 0.4 | 0.4 | 0.5 | 0.4 | 0.4 |
| | **SD** | 0.58 | 0.55 | 0.53 | 0.57 | 0.54 | 0.51 |
| | **(Min, Max)** | (0, 3) | (0, 3) | (0, 3) | (0, 3) | (0, 2) | (0, 2) |
| **Week 6** | **N** | 437 | 440 | 440 | 412 | 413 | 413 |
| | **Mean** | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| | **SD** | 0.54 | 0.54 | 0.53 | 0.59 | 0.57 | 0.55 |
| | **(Min, Max)** | (0, 3) | (0, 3) | (0, 3) | (0, 3) | (0, 2) | (0, 2) |
| **Month 3** | **N** | 432 | 432 | 431 | 408 | 408 | 408 |
| | **Mean** | 0.3 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 |
| | **SD** | 0.54 | 0.52 | 0.53 | 0.57 | 0.53 | 0.51 |
| | **(Min, Max)** | (0, 3) | (0, 3) | (0, 3) | (0, 3) | (0, 3) | (0, 2) |

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with POLYQUAD
TRAVATAN = Travoprost 40 µg/mL eye drops, solution preserved with BAK
[a]Baseline = Eligibility 2 (4 PM) Visit
SD = Standard Deviation
Hyperemia score is the average of the left and right eye scores. If only one eye is dosed then the value of the single dosed eye is analyzed.

Furthermore, changes in hyperaemia score from baseline comparing both treatments groups revealed a lower incidence of hyperaemia with Travoprost 0.003% vs Travoprost 0.004% BAK

With regards to historical data analysis (see figure below), treatment duration did not seem to have any influence in the mean ocular hyperaemia score. However, data showed that the incidence of hyperaemia seem to be higher at the beginning of the treatment. In addition, it is observed that day visits (8 AM and 10 AM) show a higher incidence of ocular hyperaemia than afternoon visits (4 PM). Regarding the mechanism of action of travoprost, these observations could be due to the maximum effect reached after 12 hours of administration, i.e. 8 AM.

**Figure 2.7.4.4–3 Mean (± SD) Hyperemia Score by Visit – C-97-71**




Data provided for ocular signs changes in study C-11-034 show that the number of patients suffering changes in ocular surface or adnexa parameters (i.e., changes in eyelid/conjunctiva and cornea) and in anterior chamber inflammation (i.e., changes in iris/anterior chamber and aqueous flare/cells) is lower with Travoprost 0.003% compared to Travoprost 0.004% BAK over the course of the study. These data reassure about the improved safety profile with a lower exposure to travoprost.

**Table 2.7.4.4–13 Number and Percentage of Patients with Ocular Signs Changes from Baseline to Any Visit – C-11-034**

| | Trav 0.003% | | | TRAVATAN | | |
|---|---|---|---|---|---|---|
| **Ocular Signs** | **Total** | **N** | **(%)** | **Total** | **N** | **(%)** |
| **Cornea** | **442** | 8 | (1.8) | **420** | 10 | (2.4) |
| **Iris/Anterior Chamber** | **442** | 1 | (0.2) | **420** | 1 | (0.2) |
| **Lens** | **442** | 4 | (0.9) | **420** | 5 | (1.2) |
| **Eyelids/Conjunctiva** | **442** | 13 | (2.9) | **420** | 21 | (5.0) |
| **Aqueous Flare** | **425** | 0 | (0.0) | **405** | 2 | (0.5) |
| **Inflammatory Cells** | **425** | 2 | (0.5) | **405** | 2 | (0.5) |

Trav 0.003% = Travoprost 30 µg/mL eye drops, solution preserved with POLYQUAD
TRAVATAN = Travoprost 40 µg/mL eye drops, solution preserved with BAK
Baseline = Eligibility 2 (8 AM) Visit
Change in ocular signs is defined as a one unit or more increase from baseline to any visit for either study eye compared to the same eye at baseline.

### Systemic adverse events

Upon CHMP request, the Applicant provided summaries of the most frequently reported systemic adverse events reported during study C-11-034. Only pruritus and rash were reported as non-

ocular adverse events related to Travoprost 0.003%. The rest of non-ocular adverse events were considered as unrelated to study treatment. Moreover, additional information related to the low systemic exposure to Travoprost 0.003% was also submitted. Therefore, proposed SmPC was considered acceptable.

### Safety in special populations

No clinically meaningful difference in the safety profile of Travoprost 0.003% compared to Travoprost 0.004% (generally, local ocular ADR consistent with the already known safety profile of topical ocular PGAs) has been identified based on a patient's age, gender, race, co-disease or concomitant medication.

### Discontinuation due to adverse events

Similar results concerning discontinuations due to an AE were observed for both treatment groups.

The majority of AEs leading to patient discontinuation were known local ocular effects associated with the use of travoprost. In addition, the number of patients that discontinued study participation due to local ocular intolerance of the study medication was similar between the treatment groups.

**Table 2.7.4.2–9 Listing of Adverse Drug Reactions Resulting in Patient Discontinuation – C-11-034**

| Inv | Pat | Treatment | Age/ Sex | Coded Adverse Event | Onset Day | Outcome of Event | Serious | C/A |
|---|---|---|---|---|---|---|---|---|
| 750 | 2252 | Trav 0.003% | 66/F | Eye irritation | 16 | Resolved wo/Tx | No | R |
| 750 | 2252 | Trav 0.003% | 66/F | Eye pruritus | 16 | Resolved wo/Tx | No | R |
| 750 | 2252 | Trav 0.003% | 66/F | Pruritus | 16 | Resolved wo/Tx | No | R |
| 1892 | 3356 | Trav 0.003% | 44/F | Myalgia | 2 | Continuing wo/Tx | No | NR |
| 5465 | 3004 | Trav 0.003% | 67/F | Conjunctival hyperaemia | 40* | Resolved w/Tx | No | R |
| 5465 | 3004 | Trav 0.003% | 67/F | Photophobia | 40* | Resolved wo/Tx | No | R |
| 5465 | 3004 | Trav 0.003% | 67/F | Vision blurred | 64 | Resolved wo/Tx | No | R |
| 1393 | 1409 | TRAVATAN | 62/F | Dizziness | 4* | Resolved wo/Tx | No | R |
| 1393 | 1409 | TRAVATAN | 62/F | Somnolence | 4* | Resolved wo/Tx | No | R |
| 3626 | 4005 | TRAVATAN | 51/F | Ulcerative keratitis | 82 | Resolved w/Tx | No | NR |
| 3627 | 4229 | TRAVATAN | 72/F | Eyelid oedema | 9 | Resolved wo/Tx | No | R |
| 3627 | 4229 | TRAVATAN | 72/F | Headache | 3 | Resolved wo/Tx | No | R |
| 3627 | 4229 | TRAVATAN | 72/F | Ocular hyperaemia | 3 | Resolved wo/Tx | No | R |
| 6099 | 1354 | TRAVATAN | 61/F | Conjunctivitis allergic | 1 | Resolved w/Tx | No | R |
| 6099 | 1354 | TRAVATAN | 61/F | Ocular hyperaemia | 1 | Resolved w/Tx | No | R |

Inv = Investigator number Pat = Patient number F= Female M = Male C/A = causality NR = Not Related
Tx = Treatment * Event occurred intermittently Coded Adverse Event = MedDRA Preferred Term (Version 14.0)
Trav 0.003% = Travoprost 0.003% Solution
TRAVATAN = Travoprost 0.004% preserved with BAK

### Post-marketing experience

On the whole, the majority of post-marketing adverse events reported with Travoprost 0.004% were local ocular effects. Several post marketing notifications of systemic adverse events were also collected. Among them, palpitations (cardiac disorder), tinnitus (ear and labyrinth disorders), nausea (gastrointestinal disorder), hypersensitivity (immune system disorder), intraocular pressure increased and blood pressure increased (investigations), headache and dizziness (nervous system disorders), insomnia and depression (psychiatric disorder), dyspnoea

and cough (respiratory, thoracic and mediastinal disorder), skin hyperpigmentation, erythema and hair growth abnormal and alopecia (Skin and subcutaneous tissue disorder) were the most frequently reported systemic AEs.

No new or relevant safety findings and no meaningful differences of adverse events for travoprost 40 µg /ml preserved with BAK, PQ or Sofzia have been found. In conclusion, post marketing data with travoprost 40 µg /ml were in accordance with the safety profile observed during the clinical trial C-11-034 and support the safety profile of Travoprost 30 µg/ml.

### 2.6.1. Discussion on clinical safety

No unanticipated safety findings for Travoprost 0.003% were identified. In the 3-month study C-11-034 involving Izba as monotherapy, the majority of AEs reported were for local ocular effects with a known causal association with the use of Travoprost and topical ocular prostaglandin analogues in general. The most common adverse reaction observed was hyperaemia of the eye (ocular or conjunctival) reported in approximately 12% of the patients.

Hyperaemia of the eye had, however, a numerically lower incidence in patients exposed to the lower strength of travoprost (i.e., 0.003%) compared to those administered Travoprost 0.004% BAK. Moreover, a lower incidence of hyperemia of the eye was observed in patients treated with Travoprost 0.003% Solution compared to historical data with Travoprost 0.004% PQ.

Therefore, no patterns has emerged over the course of Study C-11-034 that would suggest an issue concerning patient safety when dosing with Travoprost 0.003% Solution based on a review of the types and characteristics of SAEs reported and AEs leading to patient discontinuation in the study, coupled with an evaluation of overall patient characteristics. Overall, the findings with respect to SAEs and patient discontinuations from this study are in accord with historical clinical study data associated with Travoprost. Based upon a review of changes from baseline in safety assessments, no meaningful differences in visual acuity, visual fields, corneal thickness, or fundus parameters were identified. A trend towards less hyperaemia in the Travoprost 0.003% Solution treatment group was observed over the course of the study. In addition, a trend in the Travoprost 0.003% Solution treatment group towards fewer ocular sign changes from baseline in ocular surface or adnexa parameters (i.e., changes in eyelid/conjunctiva and cornea) and in anterior chamber was seen.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. Additionally, the supportive post-marketing experience with travoprost 40 micrograms/ml is also reflected in the SmPC and PL for Izba, to ensure that the most comprehensive information is made available in the product information.

### 2.6.2. Conclusions on the clinical safety

Overall, data obtained from the 3-month study C-11-034 are in general reassuring. Travoprost 0.003% seems to present a more favourable safety profile in relation to Travoprost 0.004% BAK.

Some adverse events already known for topical PGAs generally occur after several months to years of dosing (e.g.: periocular skin hyperpigmentation or discolouration, iris hyperpigmentation, and changes in eyelash characteristics). Given that these events are considered identified risks in the RMP and there is a considerable amount of data from long-term clinical studies and post-marketing surveillance with the already approved travoprost formulations, the duration of exposure is considered acceptable.

As expected, the majority of AEs reported for both treatment groups during clinical trial C-11-034 were local ocular effects and they were generally consistent with the known safety profile related to the use of travoprost and topical ocular PGAs. A reduction in the incidence of the most common adverse events (eye hyperaemia and AEs classified as ocular intolerance of travoprost) was observed when a lower concentration of travoprost was administered into the eye.

Therefore, no patterns has emerged over the course of the Study C-11-034 that would suggest an issue concerning patient safety when dosing with Travoprost 0.003% Solution or any new safety finding for established Travatan based on a review of the types and characteristics of AEs (including those leading to withdrawal from the study) or SAEs. Overall, the safety findings are consistent with historical clinical study data associated with Travatan. With regard to specific ocular safety evaluations, no meaningful differences in visual acuity, visual fields, corneal thickness, or fundus parameters were identified during the study. In fact, there was a trend towards less hyperaemia and fewer ocular sign changes from baseline in ocular surface or adnexa parameters (i.e., changes in eyelid/conjunctiva and cornea) and in anterior chamber in the Travoprost 0.003% group.

Izba is a new formulation of travoprost in which the concentration of the active has been reduced to 30mcg/ml from the 40mcg/ml previously authorised (Travatan). The indications and frequency of application remain unchanged. Given the topical nature of the product, the well-characterised therapeutic characteristics of travoprost, and the fact that the 30mcg/ml concentration in Izba represents a 25% reduction in concentration compared to the already marketed travoprost (Travatan) formulation, the CHMP considered that, following approval of Izba, the PSUR reporting should follow the one defined in the current EURD List entry for travoprost. Practically, the PSUR will combine all strengths of travoprost into one report, and a single PSUR assessment for all products containing travoprost as active substance should be followed.

## *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.

## *2.8. Risk Management Plan*

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

**PRAC Advice**

Based on the PRAC review of the Risk Management Plan version 5.0, the PRAC considers by consensus that the risk management system for travoprost (Izba) in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma is acceptable.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Summary of the Safety Concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | • Macular oedema<br>• Hyperpigmentation<br>• Hypertrichoses<br>• Iris and uveal inflammations<br>• Cardiac and vascular disorders<br>• Respiratory disorders<br>• Hypersensitivity reactions |
| Important potential risks | • Melanoma<br>• Corneal damage due to use of preserved eye drops<br>• Use during pregnancy and lactation |
| Important missing information | • Use in paediatric population<br>• Potential interactions |

The PRAC agreed.

- **Pharmacovigilance plans**

On-going and planned studies in the pharmacovigilance development plan

| **Activity / Study title (type of activity, study title [if known] category 1-3)*** | **Objectives** | **Safety concerns addressed** | **Status Planned, started,** | **Date for submission of interim or final reports (planned or actual)** |
|---|---|---|---|---|
| PIP Study C-12-009: An Open-Label, | To evaluate the steady-state plasma | Use in Paediatric Population | On-going | Final report planned 2014 |

| Activity / Study title (type of activity, study title [if known] category 1-3)* | Objectives | Safety concerns addressed | Status Planned, started, | Date for submission of interim or final reports (planned or actual) |
|---|---|---|---|---|
| Pharmacokinetic and Safety Study of Travoprost Ophthalmic Solution, 0.004% in Paediatric Glaucoma or Ocular Hypertension Patients<br><br>Category 3 | concentrations of Travoprost 0.004% PQ following once daily administration in paediatric patients with glaucoma or ocular hypertension. | | | |
| PIP Study C-12-008:<br>A 3 Month, Multicenter, Double-Masked Safety and Efficacy Study of Travoprost Ophthalmic Solution, 0.004% Compared to Timolol (0.5% or 0.25%) in Paediatric Glaucoma Patients.<br><br>Category 3 | To assess safety and efficacy of Travoprost 0.004% PQ compared to Timolol (0.5% or 0.25%) in paediatric glaucoma patients. | Use in Paediatric Population | On-going | Final report planned 2014 |

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation pharmacovigilance development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that the studies in the post-authorisation development plan are sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Summary table of Risk Minimisation Measures

| **Safety concern** | **Routine risk minimisation measures** | **Additional risk minimisation measures** |
|---|---|---|
| *Identified risks* | | |
| Macular oedema | SmPC section 4.4 (Special warnings and<br>precautions for use):<br>Caution is recommended when using Izba in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.<br><br>SmPC section 4.8. (Undesirable effects) includes macular oedema as an adverse reaction identified from post marketing experience. | None. |
| Hyperpigmentation | SmPC section 4.4 (Special warnings and<br>precautions for use):<br>“Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatmefgnt is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. The long term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. The change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e., bluebrown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Typically, the brown | None. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may be become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.<br><br>SmPC section 4.8. (Undesirable effects):<br>Very common: iris hyperpigmentation.<br>Common: eyelash discolouration.<br>Uncommon: anterior chamber pigmentation. | |
| Hypertrichoses | SmPC section 4.4 (Special warnings and<br>precautions for use):<br>Travoprost may gradually change eyelashes in the treated eye(s); these changes were observed in about half of the patients in clinical trials and include: increased length, thickness, pigmentation, and/or number of lashes.<br>The mechanism of eyelash changes and their long term consequences are currently unknown.<br><br>SmPC section 4.8. (Undesirable effects):<br>Common: growth of eyelashes.<br>Uncommon: hair texture abnormal and hypertrichosis.<br>Adverse reaction identified from post marketing experience: hair growth abnormal. | None. |
| Iris and uveal inflammations | SmPC section 4.4 (Special warnings and<br>precautions for use):<br>There is no experience of travoprost in inflammatory ocular conditions. In patients with known predisposing | None. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | risk factors for iritis/uveitis, travoprost can be used with caution.<br><br>Iritis, uveitis and iridocyclitis are included in the SmPC (Section 4.8) as uncommon events. | |
| Cardiac and vascular disorders | SmPC section 4.8. (Undesirable effects):<br>Cardiac disorders:<br>Uncommon: heart rate irregular, palpitations, heart rate decreased.<br>Adverse reactions identified from post marketing experience: bradycardia, tachycardia.<br>Vascular disorders:<br>Uncommon: blood pressure decreased, blood pressure increased, hypotension, hypertension. | None. |
| Respiratory disorders | SmPC section 4.8. (Undesirable effects):<br>Uncommon: dyspnoea, asthma, respiratory disorder, oropharyngeal pain, cough, dysphonia, nasal congestion, throat irritation. Adverse reactions identified from post marketing experience: asthma aggravated. | None. |
| Hypersensitivity reactions | Hypersensitivity to the active substance(s) or to any of the excipients is included SmPC section 4.3. as a contraindication.<br>In SmPC section 4.4 (Special warnings and precautions for use) it is also stated that Izba contains propylene glycol, which may cause skin irritation and polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions.<br>In addition, hypersensitivity, drug hypersensitivity, seasonal allergy, dermatitis allergic, periorbital oedema and dermatitis contact are included as | None. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | uncommon undesirable effects in SmPC section 4.8. | |
| *Potential risks* | | |
| Melanoma | SmPC section 4.4 (Special warnings and precautions for use):<br>Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. The long term effects on the melanocytes and any consequences thereof are currently unknown. | None. |
| Corneal damage due to use of preserved eye drops | SmPC section 5.1. states that Travatan preserved with polyquaternium-1 induced minimal ocular surface toxicity, compared to eye drops preserved with benzalkonium chloride, on cultured human corneal cells and following topical ocular administration in rabbits. | None. |
| Use during pregnancy and lactation | SmPC section 4.4 (Special warnings and precautions for use):<br>Prostaglandin analogues are biologically active materials that may be absorbed through the skin. Women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In the unlikely event of coming in contact with a substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately.<br><br>SmPC section 4.6 (Fertility, Pregnancy and lactation:<br><u>Women of childbearing potential/ contraception</u><br>Travoprost must not be used in women<br>of child bearing age/potential unless | None. |

| Safety concern | Routine risk minimisation measures | Additional risk minimisation measures |
|---|---|---|
| | adequate contraceptive measures are in place (see section 5.3).<br>Pregnancy<br>Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child. Travoprost should not be used during pregnancy unless clearly necessary.<br>Breastfeeding<br>It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. The use of travoprost by breast-feeding mothers is not recommended. | |
| *Missing information* | | |
| Use in paediatric population | SmPC section 4.2 (Posology and method of administration):<br>Paediatric population<br>The efficacy and safety of travoprost in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data become available. | None. |
| Potential interactions | SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction): No interaction studies have been performed. | None. |

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

The CHMP endorsed this advice without changes.

## *2.9. User consultation*

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Travatan. The bridging report submitted by the applicant was considered to be acceptable.

# 3. Benefit-Risk Balance

***Benefits***

Alcon developed a formulation of travoprost with a reduced concentration of active substance (30 μg/mL instead of 40 μg/mL) to be dosed once-daily in the evening in patients with open-angle glaucoma or ocular hypertension. In the study conducted in support of the MA application (C-11-034), Travoprost 0.003% showed to have a similar IOP lowering efficacy to that achieved by the 0.004% concentration.

**Beneficial effects**

Overall, data indicate that Travoprost 0.003% presents a similar IOP lowering efficacy and a more favourable safety profile in relation to Travoprost 0.004% with BAK. A lower incidence of adverse drug reactions was reported when the lower concentration of travoprost was administered into the eye.

**Uncertainty in the knowledge about the beneficial effects**

The main proof of efficacy of this application is constituted be the demonstration of non-inferiority of the new formulation (Travoprost 0.003%) versus Travoprost 0.004% (Travatan) preserved with benzalkonium chloride (BAK). However, the Travatan formulation was modified in 2010 in order to replace BAK with polyquaternium-1 (POLYQUAD, PQ). Thus, the comparator used in the pivotal trial does not exactly correspond to that of the Travatan currently available on the market. The two Travoprost 0.004% formulations (BAK and PQ preserved) have, however, previously demonstrated to have similar IOP lowering effect, so that the similarity between Travoprost 0.004% PQ and Travoprost 0.003% PQ could be reasonably extrapolated.

***Risks***

**Unfavourable effects**

Data from study C-11-034 revealed that Travoprost 0.003% may cause eye hyperaemia as the most common adverse event. In addition, eye irritation, eye pain, eye pruritus, eyelids pruritus and foreign body sensation in eyes (classified as 'ocular intolerance') were also reported as adverse events related to travoprost. These AEs are compatible with the already known safety profile of Travoprost 0.004% and with the known effects derived from the use of topical ocular PGAs.

The Applicant identified the following important risks, for which adequate risk minimisation measures have been set in the Risk Management Plan

- Macular oedema
- Hyperpigmentation
- Hypertrichoses
- Iris and uveal inflammations

- Cardiac and vascular disorders
- Respiratory disorders
- Hypersensitivity reactions

**Uncertainty in the knowledge about the unfavourable effects**

A direct comparison to the current formulation available in the market (Travoprost 0.004% PQ preserved) was lacking. However, the indirect evidence provided by the equivalence between both Travoprost 0.004% formulations (BAK and PQ preserved) was considered sufficient to overcome this uncertainty.

**Benefit-risk balance**

***Discussion on the benefit-risk balance***

Izba (Travoprost 0.003%) presents a similar IOP lowering efficacy and a more favourable safety profile in relation to Travoprost 0.004% with BAK. A lower incidence of adverse drug reactions was reported when the lower concentration of travoprost preserved with PQ was administered into the eye, indicating that Izba may have a more favourable safety profile to the one of Travoprost 0.004% preserved with BAK.

However, given the proven equivalence between the Travoprost 0.004% formulations (BAK and PQ preserved) the above constitutes indirect evidence that Izba may have a more favourable safety profile overall in relation to Travoprost 0.004%.

Given that the co-existence of Izba and Travatan on the market is likely to be approximately 3 years, upon CHMP request, the Applicant provided an outline of the activities intended to minimise the potential risk of confusion for prescribers and patients. These measures are related to different packaging and trade name for each product as well as education concerning the co-existence of the two products on the market.

Adequate wording reflecting the data submitted is included in the relevant sections of the SmPC and PL.

# 4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the risk-benefit balance of Izba for decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to medical prescription.

***Conditions and requirements of the Marketing Authorisation***

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.