SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Travatan. This scientific discussion has been updated until 1 November 2003. For information on changes after this date please refer to module 8B.

1. Introduction

Travoprost is a prostaglandin analogue intended for use to reduce intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The product is presented in a concentration of 40 µg/ml of preserved eye drops (0.004%). The dose is one drop of Travoprost Eye Drops in the conjunctival sac of the affected eye(s) once daily. Travoprost Eye Drops contains travoprost (AL-6221), a prostaglandin analogue, in a sterile ophthalmic solution formulation and it is a selective, full agonist for the FP prostanoid receptor. FP receptor agonists are reported to reduce IOP by increasing uveoscleral outflow.

Rationale for the product
Glaucoma is the leading cause of irreversible blindness in the world. It is a frequent disease and it has been estimated that 66.8 million have glaucoma, 6.7 million of whom are bilaterally blind. Open angle glaucoma is the most common type, mainly primary but also, in some cases, open angle glaucoma is secondary to the exfoliation syndrome or other primary ocular diseases. Glaucoma is an optic neuropathy that leads to loss of optic-nerve tissue with an excavation of the ophthalmoscopically visible optic nerve head and consequently, to a progressive loss of vision. The elevated IOP is the main risk factor for its development and reduction of IOP has been demonstrated to protect against further damage to the optic nerve, even in patients with IOP that is statistically "normal" (so called normal tension glaucoma).

Up to 10% of people over 40 years of age have IOPs above 21 mmHg (normal range 10 to 21 mmHg); those who have such high pressures but no optic-nerve damage are considered to have ocular hypertension. In medical practice, patients who have ocular hypertension should be periodically examined (optic nerve, visual fields) to determine whether there is evidence of a progressive damage which would indicate the need to start with treatment. However, a high IOP without optic-nerve damage, in some cases (e.g. additional risk factors for glaucoma) may be treated.

The current therapeutic approach in open angle glaucoma is focused on lowering IOP by pharmacological means, surgically, or with laser therapy. Although different priorities may be given to the laser therapy, it is generally accepted that pharmacological treatments should be the first step, moving to laser trabeculoplasty as an alternative when medical treatment, often in combination, has failed or is unsuitable. Filtering surgery is usually done as the last step, after the previous approaches have failed. The initial target IOP for each patient is chosen individually according to the current amount of optic damage and the pressure at which the damage occurred, but it will be further adjusted according to the disease progression in subsequent examinations of visual field. Although different clinical aspects will guide the choice of the target initial pressure, it is common to pursue a decrease of the IOP between 20% and 40% depending on the degree of associated damage. Once the patient has achieved a “safe” IOP at which the disease does not progress, additional lowering of the IOP would provide marginal benefit entailing a higher risk of adverse reactions.

Medical treatment is initiated with a topical drug, a beta-blocker if contraindications are not present, and if necessary, a second topical drug is added or tested in monotherapy. The possible second line drugs are alpha-adrenergic agonists (such as brimonidine or apraclonidine), carbonic anhydrase inhibitors (such as dorzolamide or brinzolamide) and prostaglandin agonists (such as latanoprost). Other treatments such as topical cholinergic agonists or systemic carbonic anhydrase inhibitors have a more limited value. Beta-blockers, and particularly timolol, which is the most popular product, have an excellent pressure-lowering efficacy, long duration of action and a few ocular side effects. However, systemic side effects of topical beta blockers (bronchospasm and cardiac side effects) may limit its use in special populations (patients suffering from asthma, chronic obstructive pulmonary disease, bradycardia, elderly.). In those patients, alpha-adrenergic agonists are being increasingly used

as the first treatment as are carbonic anhydrase inhibitors. Both types of drugs are efficacious in lowering IOP and their main side effects are ocular.

Prostaglandin analogues are the most recent pharmacological group to treat topically open angle glaucoma. Instead of decreasing the production of aqueous humor produced by the ciliary body, as the above-mentioned pharmacological treatments, these products lower the IOP by means of increasing the aqueous humor outflow through the uveoscleral pathway.

Prostaglandin analogues were not initially recommended for first-line therapy due to lack of long-term experience with this new class of medication, especially regarding safety issues. These safety issues were mainly the iris pigmentation changes, the eyelash changes and the occurrence of macular oedema. All these adverse events are known to be associated with prostaglandin analogues and they precluded the first line indication. TRAVATAN (travoprost 40 microg/ml) therefore initially gained Marketing Authorisation with a second line indication:

"Decrease of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma who are intolerant or insufficiently responsive to another intraocular pressure lowering medication, as monotherapy or as adjunctive therapy."

However, the Marketing Authorisation Holder subsequently submitted a Type II variation to extend the indication to first line therapy and the following indication was accepted based on better understanding of the mechanism of action of prostaglandin analogues, as well as reassuring long term efficacy and safety data:

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

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

Travatan eye drops are formulated as 0.004% sterile, preserved, isotonic, multidose ophthalmic solutions using well-known excipients. They contain 40 micrograms of travoprost per ml of solution. A mixture of benzalkonium chloride, sodium edetate and boric acid is used as a preservative system. Polyoxyl hydrogenated castor oil 40 (HCO-40) is used as surfactant.

The container, a 2.5 ml bottle consists of a novel natural syndiotactic polypropylene (sPP), with a conventional polypropylene dispensing plug, and a white polypropylene closure. Each filled and sealed bottle is placed in a foil overwrap to preserve shelf life.

Active substance

Travoprost (INN) is a new active substance, a prostaglandin analogue ester prodrug of the active moiety (+)-fluprostenol. The molecule has 5 chiral centres and two double bonds.

Travoprost is (5Z,13E)-(9S11R,15R)-9,11,15-trihydroxy-16-(m-trifluoromethylphenoxy)-17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester.
Hydrolysis of Travoprost 40 μg/ml gives the equivalent of 36,6 micrograms /ml of (+)-fluprostenol.

Information on the active substance has been supplied in the form of an EDMF.

The commercial manufacturing process is carried out in four main stages. Four compounds are designated as starting materials: 4-(m-trifluorophenoxy)-3-hydroxy-1-butyne (CH4060), bicyclo [3,2,0] hept-2-en-6-one (CH4065), (4-caboxybutyl) triphenylphosphonium bromide, and 2-iodopropane.
The route of synthesis, elemental analysis, IR, UV/VIS, two-dimensional NMR, 1H-NMR, 13C-NMR and HPLC/mass spectrometry, have confirmed the chemical structure of travoprost, with regard to chirality and double bond configuration.

A detailed description of the manufacturing process was provided including reaction conditions, quantities of materials and yields, as well as process and chemical flowchart.

The main impurities identified are the C5-C6 trans isomer, and the travoprost free acid, synthetic by-products.
The impurity limits in the specifications are justified by toxicological studies.
The residual solvent specified, ethyl acetate (class 3 solvent used in purification) is checked by GC-FID. During the manufacturing process other solvents are used, but only ethyl acetate and 1-butanol were detected in batches. The absence of benzene in the active substance is supported by the data submitted and will be checked in the first three production batches.

Potential trace lithium from a reagent was not detected. Trace metals analysis was carried out. These analyses included zirconium, magnesium and copper, which are used in the synthetic process. These metals were not found above detection limit (Cu, Mg, Zr <13ppm)

The analytical methods used in routine controls are suitably described. Related substances and assay are carried out using the same HPLC methods, using a isocratic elution system and UV detection at 220 nm

A specific optical rotation test is included in the routine controls and the diastereomeric purity is controlled by a suitable HPLC method.

Analytical results of three batches of active substance manufactured by the current process met the proposed specifications, and show satisfactory uniformity.

The stability studies have generally been performed under ICH Q1A conditions, and 4ºC/ 35%RH. At the condition 40ºC / 75% RH only a batch was studied.

Other ingredients

All the excipients are controlled by monographs in the Ph Eur, except Polyoxyl hydrogenated castor oil 40 (Polyoxyl HCO 40), which meets the requirements of the Japanese Pharmaceutical excipients monograph (JPE). This grade material was chosen because it contains a lower content of free PEG, and is considered to be acceptable.

None of the excipients are derived from materials of animal or human origin or come into contact with such materials during their manufacture, and satisfactory certificates of analysis are presented for all the excipients.

The specifications for all excipients except strong acids and bases include microbiological contamination with limits of 100 cfu per g or ml except in the case of purified water where the limit is 1 cfu/100 ml.

Product development and finished product

Formulations containing 0 to 0.006% travoprost were developed for clinical studies, with the same composition of the formulation proposed for marketing. The supply of the active substance as oil implied the necessity of a surfactant (castor oil) in the formulation as a solubilising agent. The trometamol/borate/mannitol buffer system was selected to also provide the correct osmolality and support the preservative.

Benzalkonium chloride (BAC) was chosen as the preservative on the basis of its well-established use in eye preparations. The concentration of 0.015% was selected on the basis of stability data and satisfactory preservative efficacy testing and is within the range typically used in eye preparations.

However, the addition of boric acid and disodium edetate was necessary to aid preservation against gram-negative bacteria and fungi respectively. The final formulation meets Ph Eur Criteria A for initial and 52 week stability samples.

Sterile filtration was selected as the manufacturing process because terminal sterilisation led to deformation of the packaging components and unacceptable degradation of the active ingredient.

Development of the novel container

Standard low-density polyethylene (LDPE) 'DROP-TAINER' bottles resulted in adsorption of the active ingredient and classical polypropylene (PP) containers were considered insufficiently 'squeezable'. A new resin class, syndiotactic polypropylene (sPP) was used in the place of the more traditional resin due to its modest increase in flexibility and a lower rate of moisture transmission than LDPE.

The drop-size has been evaluated and averages 25 microlitres. It remains consistent when 64 doses, equivalent to one month's use in both eyes, are dispensed.

Manufacturing process

Initial compounding comprises dissolution of travoprost stock solution, BAC solution and HCO-40 trometamol, boric acid, mannitol and disodium edetate in purified water. Water to 90% final volume is added and the pH adjusted. The solution is sterile filtered through two 0.22 micron filters before making up to the final volume with water also passed through the sterilising filters. The Ethylene oxide pre-sterilised bottles are aseptically filled and plugs and closures fitted before labelling and packaging.

Appropriate in-process controls are in place. The analytical results for three 50 or 100 litre batches of finished product showed that the manufacturing process is adequately controlled.

Product specifications

The finished product specification is acceptable for a product of this type, and comprises tests for identity and assay of active ingredient; degradation products; identity and assay of benzalkonium chloride, boric acid and disodium edetate pH osmolality colour and clarity of solution (Ph Eur); particulates (Ph Eur); sterility (Ph Eur) and fill volume (results of gravimetric in-process control).

Travoprost is identified by TLC and RP-HPLC and assayed by the same HPLC method. Three degradation products are named in the specification: AL-5848, AL-12419 and AL-12535.

Unspecified degradation products are reported and an upper limit for individual unspecified impurities is set. This product meets ICH impurity guidelines.

Stability of the product

Three batches have been placed on stability trial. A variety of storage conditions have been studied: long-term at 25ºC/40%RH (52 weeks); accelerated at 40ºC/15%RH and 30ºC/40%RH; accelerated light conditions with and without carton; 4ºC/35%RH and freeze-thaw cycles.

The stability data support the shelf life as can be found in the SPC with no special storage precaution and a shelf life after first opening of 28 days.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

Pharmacodynamic studies have been carried out to assess the potency and selectivity of travoprost in reducing intra ocular pressure (IOP) and improving optic nerve head blood flow (ONHBF). The exact mechanism(s) by which travoprost reduces IOP has not been fully elucidated to date. It is known that $PGF_{2\alpha}$ and latanoprost, a $PGF_{2\alpha}$ analogue, increase aqueous humour outflow through the uveoscleral pathway in the cynomolgus monkey and man. Travoprost (AL-6221), a synthetic prostaglandin $PGF_{2\alpha}$ analogue, is a pro-drug of its free-acid active form (AL-5848), a selective and potent full agonist of the prostaglandin FP receptor. Travoprost by analogy to the action of $PGF_{2\alpha}$ and latanoprost is anticipated to lower IOP by an action on uveoscleral outflow.

In vitro studies

The receptor binding affinity of travoprost has been studied in the bovine corpus luteum assay, ligand binding assays, and FP mediated stimulation of phosphoinositol turnover. The potency and agonist activity of travoprost has been compared to other prostanoids such as latanoprost and unoprostone. Travoprost was observed to be a selective agonist at the FP prostanoid receptor. Compared to latanoprost and unoprostone, the free acid (AL-5848) of travoprost was observed to have higher potency, greater selectivity and full agonist properties for the prostaglandin FP receptor.

In vivo studies

The ability of travoprost to reduce IOP was evaluated in ocular hypertensive monkeys using a multiple dose protocol. Travoprost significantly reduced IOP in monkeys after once and twice daily administration. IOP response was sustained through 24 hours, and returned to baseline by 48 hours after the last once daily instillation of travoprost. An increase in ONHBF was evident in rabbits after topical administration of travoprost for seven days. No effects on systemic blood pressure, heart rate or acid-base status were observed. A single subcutaneous dose of vehicle or travoprost produced no significant changes in the electroretinogram in rabbits. This finding suggests that travoprost produces no functional changes in the photoreceptors or the inner retinal layers of the eye at doses approximately 2000-fold higher than the maximum recommended clinical dose.

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, potential for pharmacodynamic drug interactions is low.

General and safety pharmacology programme

Ocular effects
In rabbits, travoprost produced a significant incidence of hyperaemia (~30%) during the first two hours following ocular instillation. However, at five hours after dosing conjunctival hyperaemia could no longer be detected. Hyperaemia can result from a vasodilatory effect of different agents and this finding has been also observed with other locally applied prostanoids.

Systemic Effects
Although systemic exposure to travoprost, or its active free-acid form, is likely to be negligible, a thorough investigation of systemic pharmacology has been undertaken, with evaluation of potential effects on the CNS, cardiovascular system, respiratory system, gastrointestinal system, renal system and the uterus.

CNS effects in mice using doses of up to 30 µg/kg of travoprost were minimal. In the rat, at i.v. doses of up to 250-fold in excess of the therapeutic clinical dose, travoprost produced no significant effects on the cardiovascular system of rats. In the dog, similar i.v. doses of travoprost and its free acid form produced significant changes in all cardiovascular parameters (29-50% increase in cardiac

contractility). The responses were much attenuated at lower i.v. doses. Tests in dog cardiac Purkinje fibers showed that travoprost has no biologically meaningful effect on action potential duration, resting membrane potential, maximum rate of depolarization or upstroke amplitude. These *in vitro* results suggest no significant potential for QT interval prolongation by travoprost in clinical use.

Travoprost given i.v. to guinea pigs or to rats produced no meaningful effects on the respiratory or renal systems, respectively. Effects on GI propulsion and induction of uterus contraction occurred as a result of the prostanoid receptor agonist activity of AL-5848. However, the doses/concentrations required to produce such effects were many fold higher than those anticipated in clinical use.

Pharmacokinetics

The absorption, distribution, metabolism and excretion of travoprost have been studied in rats by administration of [^{3}H]-travoprost by the oral, i.v. and s.c. routes, and in rabbits, dogs and monkeys by the topical ocular route. The analytical method used was fully validated for precision, accuracy and stability for each species and matrix.

Absorption
After ocular topical administration, travoprost is well absorbed into the eye and systemic circulation of rabbits and dogs. Maximal concentrations in the aqueous humour and iris-ciliary body were measured at 1 hour after administration. Maximal plasma concentrations are reached at approximately 30 min after ocular administration.
The bioavailability of oral travoprost was found to be low in rats. However, with s.c. administration of travoprost, maximal plasma concentrations and AUCs increased in a dose-proportional manner. Following i.v. administration, plasma concentrations of travoprost declined in a biphasic manner with a mean elimination half-life of 15.6 minutes. A moderate volume of distribution (Vd_{beta}, 2.6 L/kg) and rapid clearance (CL_{Total}, 6.9 L/kg hr) were also found.

Travoprost was absorbed transdermally in rabbits. Therefore, although it is likely that travoprost is absorbed through human skin to a lesser extent than rabbit, this possibility is mentioned in the SPC.

Distribution
At 30 min after ocular administration of ^{3}H-travoprost to the rabbit, radioactivity was highest in the cornea > conjunctiva > iris ciliary body > aqueous humour. At 1 hour, concentrations had decreased in the cornea and conjunctiva, but increased in all other tissues. At 1-2 hours, the radioactivity concentration peaked in the aqueous humour, iris ciliary body, lens, choroid, retina and vitreous humour, and declined thereafter. The terminal half-lives of radioactivity in the cornea and lens were estimated to be *ca* 14 and 29 hours respectively.

Single or repeated-dose s.c. administration of ^{3}H-travoprost to rats produced highest radioactivity concentrations in the kidneys, liver, lung and plasma. In pregnant rats, radioactivity levels in amniotic fluid and foetal tissues were *ca* 3% of those in maternal plasma. Radioactivity was secreted in milk in lactating rats, maximal secretion occurring at 6 hours (milk:plasma radioactivity 11:1). AL-5848 was moderately (*ca* 80%) bound to plasma proteins in rat, monkey and human plasma *in vitro.*

Metabolism
Metabolism, which is the major route of elimination of both travoprost and AL-5848, has been studied in rats, dogs and monkeys. Pathways of AL-5848 metabolism resemble those of endogenous prostaglandin-F2α, including reduction of the delta 13-14 double bond, oxidation of the 15-hydroxyl and beta-oxidative cleavages of the carboxylic acid side chain

The only metabolites detected in man were the 15-oxo-1,2,-dinor compounds with a saturated and unsaturated 13,14 bond, whereas in patients with hepatic impairment the corresponding tetranor compounds were also present. All four metabolites were identified in urine/plasma in the rat. In the monkey, metabolites containing the reduced Δ-13 double bond were not detected.

Excretion
Following a single dose of ^{3}H-travoprost to rats, overall excretion of radioactivity (at 168h) was 34.6% and 74.0% in urine and faeces respectively. Only 0.3% of dose remained in the carcass. Using a similar dosing regimen in bile-duct cannulated rats, 54% of dosed radioactivity was recovered in bile over 72 h; 51.6% was excreted in the first 4 h.

Toxicology

Single dose toxicity
In a non-GLP ocular study in the rabbit involving the use of eye drops (containing concentrations of travoprost of up to 25 times the strength of the 0.004% solution), the treated animals showed minimal to moderate hyperaemia with a similar level of ocular discomfort, but there were no signs of systemic toxicity. I.v. administration of travoprost in the rat produced no toxic signs at 10 mg/kg, whereas mortalities occurred at higher doses, the LD_{50} being estimated as 65 mg/kg. In the mouse, i.v. doses up to 100 mg/kg resulted in no mortalities, although lethargy was apparent at 25-100 mg/kg and diarrhoea at 100 mg/kg. A similar pattern of acute toxicity has been reported for other prostanoids.

Repeated dose toxicity
Repeated-dose ocular studies in the rabbit, up to 6 months in duration, were uneventful apart from some minor changes in serum chemistry parameters. In the 6-month study, the NOAEL corresponded to *ca* 5 times the maximum intended clinical exposure. The plasma concentration of AL-5848 at 30 min after dosing was 8-18 times the clinical C_{max}. In a 12-month ocular study in the monkey, increased iris pigmentation and minor corneal epithelium surface irregularity were observed with both travoprost and the positive control latanoprost, and so appear to be class effects for $PGF_{2\alpha}$ analogues. The slight, species-specific, enlarged-eye syndrome observed with travoprost at doses similar to those intended for clinical use has also been reported for other prostanoid receptor agonists.

Repeated-dose systemic toxicity studies up to 6 months' duration in rodents were uneventful in the mouse but revealed dose-related hyperostosis and endosteal fibrosis in femur and sternum, as well as splenic extramedullary haematopoiesis in the rat. The effects on bone appear to be pharmacologically mediated and are possibly specific to the rat. At the NOAEL for effects on bone, plasma AL-5848 concentration was virtually 100 times the anticipated clinical C_{max}.

Genotoxicity
The standard battery of genotoxicity tests, three in-vitro and two in-vivo studies, showed no evidence of genotoxic potential. Bacterial reverse mutation assays in *S. typhimurium* and *E. coli* were negative. In one mouse lymphoma assay, there were somewhat equivocal results, but a repeat assay was negative. A mouse micronucleus assay and a rat bone marrow chromosome aberration assay, both gave negative results.

Carcinogenicity
The carcinogenic potential of travoprost has been investigated in two-year studies in rats and mice. There was no evidence of carcinogenic potential at doses up to and including 100 µg/kg/day when administered by s.c. injection to rats or mice.

Reproduction toxicity
A conventional series of reproductive toxicity studies has been undertaken in the rat and mouse. Studies in the pregnant rabbit revealed significant foetal loss. In rodents, the reproductive toxicity of travoprost was characterised by early resorptions, post-implantation loss, reduced foetal weight and increased skeletal malformations, the effects being more pronounced in the mouse than the rat. Reduced duration of gestation and adverse effects on pup survival were also observed. The effects on reproduction are those expected for the pharmacological activity of travoprost. The use of Travatan in women who are or may become pregnant should therefore be contraindicated.

Special studies
Travoprost showed no potential for delayed contact sensitisation in the guinea pig maximisation test. Furthermore, no potential of travoprost to induce a carcinogenic response was found in a SHE assay (cell transformation assay in Syrian hamster embryo cells).

An exploratory study in the rabbit demonstrated that significant systemic exposure to AL-5848 can result from dermal application of travoprost eye drops. Exposure of unprotected skin to travoprost may thus result in systemic exposure. This issue is addressed in the SPC.

Environmental risk assessment
No significant intrinsic hazardous properties have been associated with travoprost, its metabolites of degradation products, based upon a significant battery of studies in mammalian species investigating various aspects of toxicity. A Phase I environmental risk assessment showed that travoprost is likely to be well below the recommended threshold levels for the aqueous and soil compartments. Based on the data submitted, no adverse environmental effects are predicted for travoprost.

4. Part IV: Clinical aspects

All clinical trials were performed according to GPC standards and agreed international ethical principles.

Clinical pharmacology

Pharmacodynamics

In a dose finding study (C-97-02), Travoprost was found to reduce intraocular pressure (IOP) in man about two hours after administration, and its maximum effect (-6.6 to -8.5 mmHg) was reached after approximately twelve hours. IOP reduction with travoprost was maintained for at least 24 hours.
The exact mechanism(s) by which travoprost reduces IOP has not been fully elucidated to date. Drugs that lower IOP either decrease the formation rate or increase the drainage rate of aqueous humour. It is known that $PGF_{2\alpha}$ and latanoprost, a $PGF_{2\alpha}$ analogue, increase aqueous humour outflow through the uveoscleral pathway in the cynomolgus monkey and man. Travoprost, a synthetic prostaglandin $PGF_{2\alpha}$ analogue, is a prodrug of a highly selective, potent (K_i= 52 nM), full agonist of the prostaglandin FP receptor. Thus, travoprost, by analogy to the action of $PGF_{2\alpha}$ and latanoprost, is anticipated to lower IOP by an action on uveoscleral outflow. The IOP lowering effect of travoprost has been assessed in two dose-finding (Studies C-96-52 and C-97-02). These studies are described under *Dose response studies and main clinical studies.*

Pharmacokinetics

The clinical pharmacokinetics of travoprost has been investigated in three multiple dose topical ocular studies: Studies C-99-08, C-99-97 and C-00-05. Study C-99-08 was conducted in normal volunteers to characterise the steady-state pharmacokinetics of Travoprost and AL-5848 acid metabolite following topical ocular administration of Travoprost 0.004% and Travoprost 0.0015%. Study C-99-97 was conducted in subjects with normal renal function or renal impairment. The objective was to characterise the steady-state pharmacokinetics of Travoprost and its acid metabolite (AL-5848) following topical ocular administration of Travoprost 0.004%. Study C-00-05 was carried out in subjects with normal hepatic function or hepatic impairment.

Following once daily topical ocular administration of Travoprost 15 µg/ml and 40 µg/ml Eye Drops to healthy volunteers (Study C-99-08) for 7 days, low systemic exposure to AL-5848 was demonstrated. Peak AL-5848 plasma concentrations of 25 pg/ml or less were observed between 10 and 30 minutes post-dose. Thereafter, plasma levels declined rapidly to below the 10 pg/ml assay quantitation limit at 1 hour post-dose. Due to the low plasma concentrations and rapid elimination following topical dosing, the elimination half-life of AL-5848 in man could not be determined. The similarity of AL-5848 plasma concentrations on Day 1 and Day 7 would indicate no plasma accumulation.

Metabolism is the major route of elimination of both travoprost and AL-5848. *In vivo* and *in vitro*, travoprost is rapidly hydrolysed to AL-5848 by esterases. The metabolic pathway of AL-5848

parallels that of latanoprost and endogenous $PGF_{2\alpha}$, which is characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and β-oxidative cleavages of the upper side chain.

In order to assess potential clinical exposure to travoprost metabolites, plasma samples from subjects with severe renal impairment (C-99-97) and severe hepatic impairment (C-00-05) were screened by HPLC/MS/MS. Overall, these findings indicate negligible levels of metabolites in human plasma even in subjects with severely compromised renal or hepatic function. There seems to be no necessity to adjust the dose when travoprost is administered to patients with diverse degree of renal or hepatic impairment.

No specific pharmacokinetic studies have been performed in patients under 18 years of age.

Interaction studies

No studies evaluating drug-drug interactions have been performed. Since travoprost undergoes a biotransformation pathway similar to endogenous prostaglandin-F2α, and since systemic levels of active metabolite following topical ocular administration are negligible, interactions with concomitant medications in patients receiving topical ocular doses is unlikely. *In vitro* experiments have shown the travoprost free acid to be moderately bound (about 80%) to plasma proteins in humans, indicating drug-drug interactions through protein binding to be unlikely.

Clinical efficacy

The application consisted of a total of 10 complete trials: two phase I studies, two phase II studies and six phase III studies. The phase II/III studies included the two main dose-finding phase II studies (C-96-52, C-97-02) and three pivotal phase III monotherapy studies (C-97-71, C-97-72, C-97-79) and one pivotal phase III study in adjunctive therapy with timolol (C-97-73). There were two additional studies for efficacy and safety: one phase II plus brimonidine and one phase III open label. In addition to these complete studies, seven ongoing studies were included in the submission. The target population included in pivotal trials was males and females of any race, aged 63,8 (mean) diagnosed of open-angle glaucoma (with or without pigment dispersion or pseudoexfoliation component) or ocular hypertension. Patients in pivotal trials were required to have open-angle glaucoma or ocular hypertension with an IOP of 24-36 mmHg at 8/9 a.m., and 21-36 mmHg at 10/11 a.m and 21-36 mmHg at 4 p.m.

Table 1. Summary of completed efficacy clinical studies with Travoprost:

Protocol Type (Number)	**Study Design**	**Treatment Duration**	**Patient Population**	**Treatment Groups**	**No**
Dose-response (C-96-52:US)	Double-blind, randomised, Placebo-controlled	28 d	OAG, OH	Travoprost 0,0001% Travoprost 0,001% Travoprost 0,002% Vehicle	138 (1:1:1:1)
Dose-response (C-97-02:US)	Double-blind, randomised, Placebo-controlled	28 d	OAG, OH	Travoprost 0,001% Travoprost 0,002% Travoprost 0,004% Travoprost 0,006% Vehicle	227 (1:1:1:1:1)
Pivotal, Efficacy/Safety (C-97-71: US)	Double-blind, randomised, Active-controlled	12 m	OAG, OH	Travoprost 0.0015% Travoprost 0.004% Latanoprost 0.005% Timolol 0.5%	801 (1:1:1:1)
Pivotal Efficacy/Safety (C-97-72: US)	Double-blind, randomised, Active-controlled	6 m	OAG, OH	Travoprost 0.0015% Travoprost 0.004% Timolol 0.5%	605 (1:1:1)

Protocol Type (Number)	Study Design	Treatment Duration	Patient Population	Treatment Groups	No
Pivotal Efficacy/Safety (C-97-73: US)	Double-blind, randomised, Placebo-controlled	6 m	OAG, OH	Travoprost 0.0015% Travoprost 0.004% Vehicle (all adjunctive to Timolol 0.5% BID)	427 (1:1:1)
Pivotal Efficacy/Safety (C-97-79: EU/Australia)	Double-blind, randomised, Active-controlled	9 m	OAG, OH	Travoprost 0.0015% Travoprost0.004% Timolol 0.5%	573 (1:1:1)
Efficacy/Safety (C-99-18)	Double-blind, randomised, Active-controlled	70 d	OAG, OH	Travoprost 0.0015% Travoprost 0.0015% +Brimonidine 0.2% vehicle	81 (2:2:1)
Efficacy/Safety (C-98-09)	Open-label	3 m	OAG, OH	Travoprost 0.004%	30

Abbreviations used include the following: PK (pharmacokinetic); OAG open angle glaucoma; OH ocular hypertension; BID (twice daily); US (United States); EU (Europe).

Dose-response studies and main clinical studies

Study C-96-52

Study C-96-52 was a four-week, randomised, double-blind, multicenter, placebo-controlled, parallel group dose-response study. The main objective of this study was to evaluate the safety and IOP-lowering efficacy of three concentrations of Travoprost Ophthalmic Solution compared to vehicle in adult patients of any race and either sex with primary open-angle glaucoma (with or without pigment dispersion or pseudoexfoliation component) or ocular hypertension. A total of 138 patients were randomised to travoprost in concentrations of 0.0001%, 0.001% and 0.002% or placebo. All groups received the topical ocular medication, one drop, once daily in each eye for 28 days. The primary efficacy variable was mean IOP reduction from a diurnally adjusted baseline in the patient's worse eye.

Results demonstrated dose-dependent IOP reductions with increasing concentrations of travoprost, which were significantly greater than Vehicle at all IOP measurement times ($p<0.02$). Overall, the greatest IOP lowering efficacy was produced by travoprost 0.002%, with IOP changes ranging from -5.6 to -7.4 mmHg with a 24-h duration of action. The results of this study suggest that the maximum effective dose was not established since there was a significant difference between 0.001% and 0.002% at the 8 AM (trough) and 10 AM time points.

Study C-97-02

This study had the same entry criteria and primary endpoint as study C-96-52. A total of 227 patients were randomised to travoprost in concentrations of 0.001%, 0.002%, 0.004% and 0.006% or placebo. All groups received the topical ocular medication, one drop, once daily in each eye for 28 days.

All four concentrations of Travoprost (0.001%, 0.002%, 0.004% and 0.006%) produced significantly greater IOP reduction than Vehicle at all IOP measurement times ($p\leq0.0001$). Travoprost 0.004% and 0.006% produced significantly greater IOP reduction relative to travoprost 0.001% at all time points ($p<0.05$). The greatest IOP lowering efficacy was produced by travoprost 0.004% with IOP changes ranging from -6.6 to -8.5 mmHg with a 24 h duration of action.

Main studies

Monotherapy

Study C-97-71

1. Description of the study
This was a 12-month, randomised, double blind, multicenter, active-controlled, parallel group study. All patients, of any race and either sex, were diagnosed with open-angle glaucoma (with or without pigment dispersion or pseudoexfoliation component) or ocular hypertension. All eligible patients were required to have post-washout IOP measurements at 8 AM of 24 mmHg to 36 mmHg, inclusive, in a least one eye (the same eye) at both eligibility 1 and 2 visits. Additionally, 10 AM and 4 PM IOP measurements were required to be 21 mmHg to 36 mmHg in a least one eye (the same eye) at both eligibility 1 and 2 visits.

Eight hundred and one (801) eligible patients who met all inclusion criteria were randomised equally into one of four treatments groups and dosed once-daily with either travoprost 0.0015% (n=205) or 0.004% (n=200) or latanoprost 0.005% (n=196) or twice daily with timolol 0.5% (n=200) for a treatment period of 12 months.

2. Primary endpoints/assays
The primary efficacy variable was mean IOP in patient's worse eye at 8 AM, 10 AM and 4 PM. IOP was measured at 8AM, 10 AM and 4 PM on week 2, month 3, month 6 and month 12 visits and at 8 AM and 10 AM on month 1.5, month 4.5 and month 9 visits.

3. Statistical analysis
All patients who received drug were considered evaluable for safety analysis. All patients who received drug and had at least one on-therapy visit were considered evaluable for intent-to-treat analysis. The primary analysis was performed on only those patients who met the protocol inclusion and exclusion criteria and on all data points ruled evaluable. The statistical objectives of this study were to demonstrate that: 1) Travoprost 0.004% is non inferior to timolol 0.5% in IOP lowering efficacy, 2) Travoprost 0.0015% is non inferior to timolol 0.5% in IOP lowering efficacy, 3) Travoprost 0.004% is non inferior to latanoprost 0.005% in IOP lowering efficacy and 4) Travoprost 0.004% is superior to travoprost 0.0015% in IOP lowering efficacy.

Hypothesis tests were performed using repeated measures ANOVA. Non-inferiority was deemed to have been established if the upper limit of the 95% confidence interval for the treatment difference between travoprost and timolol (travoprost-timolol) was less than 1.5 mmHg. Mean IOP was also estimated by the least squares means from the repeated measures analysis of variance. Descriptive statistics were calculated for IOP, IOP change from baseline, and percent change from baseline.

RESULTS

4 Study populations/accountability of patients
Eight hundred and one (801) patients were randomized to one of four treatments. All of them received active substance and were included in the safety analysis. Of the 801 randomized patients, 787 were assessed for the ITT analysis. The 14 remaining patients were excluded from the ITT analysis due to no on-treatment visit data.

Seven hundred and sixty (760) patients were included in the per protocol analysis. Protocol deviation was the reason for the remaining 41 patients not being included into the per protocol analysis.. One hundred and twenty-three (123) patients discontinued study. Main reasons were: Adverse event (47), Non-compliance (5), Inadequate control of IOP (14), Patient decision (5), Non qualifying IOP (16), Lost of follow up (10), Site closure (13), Use of contraindicated medications (6), Other (7).

5. Efficacy results
Of the 787 patients included in the ITT analysis, 392 were male and 395 were female. The mean age of the patients was 64.2 years and the ages ranged from 22 to 94. The frequencies of patients by race

were 566 Caucasian, 177 Black, 6 Asian and 38 other races as follows: 37 Hispanic and 1 Native American. The diagnoses were distributed as follows: 530 patients were diagnosed with open-angle glaucoma, 247 with ocular hypertension, 6 with pigmentary glaucoma and 4 with pseudoexfoliation glaucoma.

There were no statistically significant demographic differences among treatment groups at baseline

Travoprost (0.0015% and 0.004%) dosed once daily produced IOP reductions that were equal or superior to IOP reductions produced by Timolol 0.5% dosed twice daily at all visits over the twelve-month treatment period based on tests of non-inferiority.

Subsequent to the tests of non-inferiority, superiority of Travoprost to Timolol was demonstrated by greater IOP reductions ranging from 1.0 to 1.8 mmHg at 16 of 18 visits in the Travoprost 0.0015% group and 1.1 to 1.9 mmHg at 17 of 18 visits in the Travoprost 0.004% groups.

The IOP reductions produced by Travoprost 0.004% and 0.0015% were non inferior to those produced by Latanoprost 0.005% dosed once-daily at all visits over the twelve month treatment period. Non inferiority of travoprost (for both concentrations) vs. latanoprost was reflected by upper 95% confidence limits that were less than +1.5 mmHg at all the time points comparing the groups. The largest values for the upper 95% confidence limit were +1.08 mmHg for the comparison travoprost 0.004% to latanoprost 0.005% and +1.2 mmHg for travoprost 0.0015% to latanoprost 0.005%. Mean IOPs were lower for Travoprost (up to 0.9 mmHg for 0.0015% and up to 1.3 mmHg for 0.004%) compared to Latanoprost 0.005% at 4 of 5 visits over the first 1.5 months of therapy and the differences were statistically significant at 3 of the time points (0.004% vs. latanoprost)

The IOP reductions produced by Travoprost 0.004% were greater than those produced by Travoprost 0.0015% at most treatment visits by up to 0.5 mmHg, although these differences were not significant. The by visit analysis demonstrated that the mean IOP produced by travoprost 0.004% was lower than that produced by travoprost 0.0015% at 13 of 18 visits.

Travoprost dosed once daily produced clinically relevant and statistically significant reductions from baseline. The IOP reductions were statistically significant compared to baseline at all treatment visits and ranged from -5.9 to -7.7 mmHg in the 0.0015% group and from -6.6 to -8.0 mmHg in the 0.004% group.

The clinical relevance of the IOP reductions was further demonstrated by the percent of patients in each treatment group who responded to treatment. A clinically relevant response was considered if their IOP decreased to 17 mmHg or lower, or if their IOP decreased by 30% or more. The percentage of responders was54.7% for travoprost 0.004%, 49.3% for travoprost 0.0015%, 49.6% for latanoprost and 39.0% for timolol.

Study C-97-72

1. Description of the study

This was a 6-month, randomised, double blind, multicenter, active-controlled, parallel group study to compare the safety and efficacy of travoprost 0.0015% and 0.004% dosed once daily with timolol 0.5% dosed twice daily. This study had the same entry criteria and primary endpoint as study 97-71. Also the same hypotheses as those used in study 97-71 comparing travoprost with timolol were tested.

RESULTS

2 Study populations/accountability of patients

Six hundred and five (605) patients were randomized to one of three groups of treatments. All of them received the drug and were included in the safety analysis. Eleven patients were excluded from the ITT analysis due to no on-treatment visit data and so, 594 were included in the ITT analysis.

The PP analysis included 557 patients of the 605 randomized, since 48 patients were excluded from the PP analysis due to protocol deviations.

Five hundred and twelve (512) patients completed the study. Ninety three (93) patients discontinued study prematurely. Main reasons were: Adverse event (23), Inadequate control of IOP (8), Patient decision (5), Lost of follow up (1), Ineligible entry criteria or protocol deviation, including: Non

qualifying IOP, Use of contraindicated medications, Concurrent investigational medication, Non-compliance (56).

3. Efficacy results

Of the 594 patients included in the ITT analysis, 293 were male and 301 were female. The mean age of the patients was 63.7 years and the ages ranged from 21 to 91; 274 patients (46%) were younger than 65 years at the time of the enrolment. The frequencies of patients by race were 488 Caucasian, 63 Black, 4 Asian and 39 other races as follows: 36 Hispanic, 1 Native American, 1 Indian, and 1 Spanish/Irish. The diagnoses were distributed as follows: 382 patients were diagnosed with open-angle glaucoma, 196 with ocular hypertension, 14 with pigmentary glaucoma and 2 with pseudoexfoliation glaucoma.

There were no statistically significant demographic differences among treatment groups at baseline.
Travoprost (0.0015% and 0.004%) dosed once daily produced IOP reductions that were equal or superior to IOP reductions produced by timolol 0.5% dosed twice daily based on tests of non-inferiority. Superiority to timolol 0.5% was demonstrated at 9 of 13 (vs. 0.0015% group) and 10 of 13 (vs. 0.004%) treatment visits.

Comparisons of Travoprost vs. timolol (travoprost 0.004% vs. Timolol 0.5% and travoprost 0.0015% vs. Timolol 0.5%) were planned and carried out as tests of non inferiority. The per protocol data set was used for the non inferiority tests and the ITT data set was used for the superiority tests. For all tests, comparisons were made first between travoprost 0.004% and timolol 0.5% then travoprost 0.0015% and timolol, in accordance with the planned sequential testing strategy.

The 95% confidence limits in the PP population showed that travoprost 0.004% and travoprost 0.0015% were non inferior to timolol 0.5% at all treatments visits for both the combined and individual visit results. All the upper 95% confidence intervals were less than +1.5 mmHg, the upper limit of clinical relevance established to demonstrate non inferiority in this study. The largest value for the upper 95% confidence limit was +0.42 mmHg.
Subsequent to the tests of non-inferiority, superiority of travoprost to timolol was demonstrated by greater IOP reductions at 10 of 13 visits for the travoprost 0.004%/timolol comparison and at 9 of 13 for travoprost 0.0015%/ timolol comparison.

Travoprost (0.0015% and 0.004%) dosed once daily produced clinically relevant and statistically significant IOP reductions from baseline. IOP changes were greatest in the travoprost 0.004% group and ranged from -6.6 to -8.0 mmHg when compared to those treated with travoprost 0.0015% –-5.9 to -7.5 mmHg) and timolol (-5.2 to -7.1 mmHg).

The clinical relevance of the IOP reductions was further demonstrated by the percent of patients in each treatment group who responded to treatment. A clinically relevant response was considered if IOP decreased to 17 mmHg or lower, or if their IOP decreased by 30% or more. The percentage of responders was 50.5% for travoprost 0.004%, 45.1% for travoprost 0.0015% and 35.4% for timolol.
The IOP reductions produced by both concentrations of travoprost were maintained over the 6-month treatment period. The IOP reductions produced by Travoprost 0.004% were greater than those produced by Travoprost 0.0015% at most treatment visits by up 0.7 mmHg, although these differences were not significant. The by visit analysis demonstrated that the mean IOP produced by travoprost 0.004% was lower than produced by travoprost 0.00015% at 8 of 13 visits.

<u>*Study C-97-79*</u>

1. Description of the study

This was a 9-month, randomised, double blind, multicenter, active-controlled, parallel group study to compare the safety and efficacy of 0.0015% and 0.004% once daily travoprost with 0.5% twice daily timolol. This study had the same entry criteria and primary endpoint as study 97-71 except that measurements were taken at 9 a.m. and 11 a.m. rather than 8 a.m. and 10 a.m. Also the same hypotheses as those used in study 97-71 comparing travoprost with timolol were tested.

RESULTS

2 Study populations/accountability of patients

Five hundred and seventy-three (573) patients were randomized to one of three groups of treatments. All of them received the drug and were included in the safety analysis. One patient was excluded from the ITT analysis due to no on-treatment visit data and so, 572 were included in the ITT analysis.

The PP analysis included 507 patients of the 573 randomized, since 66 patients were excluded from the PP analysis due to protocol deviations.

Five hundred and twenty-four (524) patients completed the study. Forty-nine (49) patients discontinued study prematurely. Main reasons were: Adverse event (27), Non-compliance (3), Inadequate control of IOP (10), Patient decision (3), Lost of follow up (2), Ineligible entry criteria or protocol deviation, including women not menopausal (3), Patient moved to other location (1).

3. Efficacy results

Of the 572 patients included in the ITT analysis, 284 were male and 288 were female. The mean age of the patients was 63.3 years and the ages ranged from 31 to 88; 296 patients (52%) were younger than 65 years at the time of the enrolment. The frequencies of patients by race were 560 Caucasian, 7 Black, 4 Asian and 1 other races. The diagnoses were distributed as follows: 313 patients were diagnosed with open-angle glaucoma, 221 with ocular hypertension, 9 with pigmentary glaucoma and 29 with pseudoexfoliation glaucoma.

There were no statistically significant demographic differences among treatment groups at baseline.

Based on tests of non-inferiority, travoprost (0.0015% and 0.004%) dosed once daily produced IOP reductions that were equal or superior to IOP reductions produced by timolol 0.5% dosed twice daily. Superiority of 0.004% to timolol 0.5% was demonstrated at 9 AM, 11 AM and 4 PM, combined across all treatment visits.

The 95% confidence limits in the PP population showed that travoprost 0.004% and travoprost 0.0015% were non inferior to timolol 0.5% since intervals were less than +1.5 mmHg, the upper limit of clinical relevance established to demonstrate non inferiority in this study. The largest value for the upper 95% confidence limit was +0.88 mmHg.

Subsequent to the tests of non-inferiority, superiority of travoprost to timolol was demonstrated by greater IOP reductions at 10 of 15 visits for the travoprost 0.004%/timolol comparison.. These combined data showed that the IOP lowering efficacy of travoprost relative to timolol improves over the course of the day.

Travoprost 0.0015% and 0.004% dosed once-daily produced clinically relevant and statistically significant IOP reductions from baseline at all treatment visits. The IOP changes observed for travoprost ranged from -7.1 to -8.4 mmHg for the 0.0015% concentration and from -8.1 to -9.0 for travoprost 0.004%. These changes ranged from -6.5 to -7.9 mmHg for timolol.

The clinical relevance of the IOP reductions was further demonstrated by the percent of patients in each treatment group who responded to treatment. A response was considered clinically relevant if the IOP decreased to 17 mmHg or lower, or if their IOP decreased by 30% or more. The percentage of responders was 63.3% for travoprost 0.004%, 54.8% for travoprost 0.0015% and 47.1% for timolol. The IOP reductions for timolol in this study were similar to previously published studies.

The IOP reductions produced by both concentrations of travoprost were maintained over the 9-month treatment period. The IOP reductions produced by Travoprost 0.004% were greater than those produced by Travoprost 0.0015% at all treatment visits, with a statistically significant difference at 11 AM. The by visit analysis demonstrated that the mean IOP obtained with travoprost 0.004% was lower than mean IOP produced by travoprost 0.0015% at all treatment visits by up to 1.1 mmHg in favour of the 0.004% concentration. The combined analysis collapsed across all visits demonstrated that travoprost 0.004% had better control of IOP over the course of the day by up to 0.6 mmHg, with this difference being statistically significant at 11 AM measurement time.

Adjunctive therapy

Study C-97-73

1. Description of the study

This was a 6-month, randomised, double blind, multicenter, placebo-controlled, parallel group study. All patients, of any race and either sex, were diagnosed with uncontrolled open-angle glaucoma (with or without pigment dispersion or pseudoexfoliation component) or ocular hypertension while maintained on timolol 0.5%. All eligible patients were on timolol 0.5% therapy and were required to have 24 mmHg to 36 mmHg mean IOP at 8 AM and 21 mm Hg to 36 mm Hg at 10 AM and 4 PM on both eligibility days.

Four hundred and twenty seven (427) eligible patients who met all inclusion criteria were randomised to receive one of the following three treatments: travoprost 0.0015% once daily plus timolol 0.5% twice daily (n=142), travoprost 0.004% once daily plus timolol 0.5% twice daily (n=146) or travoprost placebo once daily plus timolol 0.5% twice daily dosed (n=139) for a treatment period of 6 months.

2. Primary endpoints/assays

IOP was measured at 8AM, 10 AM and 4 PM on week 2, month 3 and month 6 visits and at 8 AM and 10 AM on month, 1.5 and month 4.5 visits. This study had the same primary endpoint as the monotherapy studies.

3. Statistical analysis

All patients who received drug and had at least one on-therapy visit were considered evaluable for safety and intent-to-treat analysis. The primary analysis was performed on only those patients who met the protocol inclusion and exclusion criteria and on all data points ruled evaluable. The statistical objectives of this study were to demonstrate that: 1) Travoprost 0.004% is superior to vehicle in IOP lowering efficacy, 2) Travoprost 0.0015% is superior to vehicle in IOP lowering efficacy and 3) Travoprost 0.004% is superior to travoprost 0.0015% in IOP lowering efficacy

Tests of hypotheses were performed using repeated measures analysis of variance. The family-wise error rate for testing multiple hypotheses between the travoprost and placebo treatments groups was controlled at alpha =0.05. Descriptive statistics were calculated for IOP, IOP change from baseline, and percent change from baseline. Mean IOP was also estimated by the least squares means from the repeated measures analysis of variance.

RESULTS

4 Study populations/accountability of patients

Four hundred and twenty seven (427) patients were randomized to one of three groups of treatments. Of these all but one (426) were included in the safety analysis. The patient who was excluded from the safety analysis did not receive the study medication. Seventeen patients were excluded from the ITT analysis due to no on-treatment visit data and therefore, 410 were included in the ITT analysis. The PP analysis included 362 patients randomized, since 65 patients were excluded from the PP analysis due to protocol deviations. Three hundred and forty nine (349) patients completed the study. Seventy eight (78) patients discontinued study prematurely. Main reasons were: Adverse event (16), Non-compliance (3), Inadequate control of IOP (24), Patient decision (4), Lost of follow up (4), Ineligible entry criteria or protocol deviation (27).

5. Efficacy results

Of the 410 patients included in the ITT analysis, 180 were male and 230 were female. The mean age of the patients was 63.7 years and the ages ranged from 11 to 89; 206 patients (50.2%) were younger than 65 years at the time of the enrolment. The frequencies of patients by race were 283 Caucasian, 94 Black, 3 Asian and 30 other races as follows: 29 Hispanic and 1 Cuban. The diagnoses were distributed as follows: 360 patients were diagnosed with open-angle glaucoma, 35 with ocular hypertension, 7 with pigmentary glaucoma and 8 with pseudoexfoliation glaucoma.

There were no statistically significant demographic differences among treatment groups at baseline.

Travoprost (0.0015% and 0.004%) dosed once daily produced statistically superior additional IOP reductions compared to Vehicle at all treatment visits when used adjunctively with Timolol 0.5% dosed twice daily.

The difference between travoprost 0.004% and vehicle ranged from 4.2 mmHg to 5.0 mmHg, and the difference between travoprost 0.0015% and vehicle ranged from 3.7 mmHg to 4.5 mmHg.

The 95% confidence limits showed that travoprost 0.004% and travoprost 0.0015% were superior to vehicle at all treatments visits for both the combined and individual visit results. All the upper 95% confidence interval were less than 0 mmHg and the p-values also showed that both concentrations of travoprost were superior to vehicle in IOP lowering efficacy.

Travoprost (0.0015% and 0.004%) dosed once daily in the evening produced clinically relevant and statistically significant IOP reductions from baseline when used adjunctively with Timolol 0.5% dosed twice daily. The IOP changes observed for the travoprost 0.0015% group ranged from -5.1 to -6.7 mmHg and from -5.7 to -7.2 mmHg for travoprost 0.004%.

The clinical relevance of the IOP reductions was further demonstrated by the percent of patients in each treatment group who responded to treatment. A patient was considered to have a clinically relevant response if IOP decreased by 6 mmHg or more, or if their IOP decreased to 20 mmHg or lower. The percentage of responders was 66.4% to 86.9% for travoprost 0.004%, 66.2% to 82.7% for travoprost 0.0015% and 23.1% to 43.3% for placebo.

The IOP reductions produced by both concentrations of travoprost were maintained over the 6-month treatment period when used adjunctively with timolol 0.5%.
The IOP reductions produced by Travoprost 0.004% dosed once-daily were marginally greater than those produced by Travoprost 0.0015% at all treatment visits when used adjunctively with timolol 0.5% dosed twice-daily with a maximum difference of 1.1 mmHg in favour of the 0.004% concentration (at month 1.5, 8AM; p=0.0293).

Clinical studies in special populations

Patients with renal impairment

One study has been performed in patients with renal impairment (C-99-97) in order to assess the pharmacokinetic parameters in subjects with normal and impaired renal function. (see section pharmacokinetics). No efficacy parameters were measured in this trial. The results of this trial showed that travoprost 0.004% did not accumulate in patients with several degrees of impaired renal function. There is thus no pharmacological reason to think that efficacy in patients with impaired renal function would be different from patients with normal renal function.

Patients with hepatic impairment

One study has been performed in patients with hepatic impairment (C-00-05) in order to assess the pharmacokinetic parameters in subjects with normal and impaired hepatic function. The results of this trial showed that travoprost 0.004% did not accumulate in patients with impaired hepatic function. There is thus no pharmacological reason to think that efficacy in patients with impaired hepatic function would be different from patients with normal hepatic function.

Supportive studies

The applicant submitted also a study with combined administration treatment of Travoprost/Brimonidine (C-99-18) which provides additional information on the additive effect of Travoprost with other anti-glaucomatous agents. Additionally, the Applicant reported one open-label, monotherapy study (C-98-09) conducted in Mexico, in which patients were treated with Travoprost 0.004% dosed once daily.

Study C-99-18

This phase II double-blind, multicenter, parallel group study randomised 81 patients to one of three treatments: travoprost 0.0015% once daily/travoprost 0.0015% BID + brimonidine 0.2% BID (n=33); Travoprost 0.0015% once daily/ travoprost 0.0015% BID (n=32); travoprost 0.0015% once daily/

travoprost vehicle BID (n=16). All patients were dosed with travoprost 0.0015% once daily for four weeks in the run-in period (phase I). The duration of the concomitant therapy phase (phase II) was 6 weeks.

The main criteria for inclusion was identical to pivotal trials in monotherapy (see above).

Concomitant twice daily dosing of Travoprost 0.0015% plus Brimonidine resulted in greater IOP-lowering efficacy than twice daily dosing of Travoprost 0.0015% alone. These differences in favour of Travoprost plus Brimonidine were 0.68, 3.75, and 1.24 mmHg at 8:00 a.m., 10:00 a.m. and 4:00 p.m, respectively, and were clinically relevant and statistically significant at the 10:00 a.m. and 4.00 a.m. time points. Both once and twice daily dosed Travoprost 0.0015% produced clinically relevant and statistically significant reductions in IOP ranging from 5.38 to 7.06 mmHg and from 4.47 to 6.47 mmHg, respectively. Switching from once to twice daily dosing of Travoprost 0.0015% resulted in 0.59 to 0.91 mmHg less IOP reduction.

Study C-98-09

This open label study included 30 patients with open-angle glaucoma (with or without a pseudoexfoliation or pigment dispersion component) or ocular hypertension. Patients received travoprost 0.004% dosed once daily; one drop in each eye (at 8 PM), for three months.

The primary efficacy variable was mean IOP change from baseline at the 8 AM time points for the patient's worse eye as defined earlier. Repeated measures analysis of variance was used to test IOP measurements against a pre-treatment baseline. Additionally, descriptive statistics were calculated for IOP, IOP change from baseline, and IOP percent change from baseline.

The efficacy results presented are based primarily upon the per protocol data set of 29 patients. IOP changes from baseline for Travoprost 0.004% were clinically relevant and statistically significant at all treatment visits with the changes ranging from -8.2 to -8.9 mmHg. The clinical relevance of the IOP reductions was demonstrated by the percentage of patients who responded to treatment. Patients were considered to have a clinically relevant IOP response to treatment if their IOP decreased by 6 mmHg or more, or if their IOP decreased to 20 mmHg or lower. The percentage of patients with a clinically relevant IOP response to treatment based on these criteria ranged from 95.8% to 100% .

Discussion on clinical efficacy

Three pivotal studies (C-97-71, C-97-72, C-97-79) have been performed in order to assess the IOP lowering efficacy of travoprost. All of them compared travoprost in concentrations of 0.0015% and 0.004% to timolol 0.5%, which is the standard therapy of glaucoma. One of the three trials included also an additional arm with latanoprost, which is the only approved product in the same pharmacological group in Europe. The design of all three trials is an accepted design for the development of antiglaucoma products and the selected population is representative of the target population although most patients have their IOP close to the lower limit of the inclusion criteria.

The main hypothesis in all trials was the demonstration of non-inferiority versus active comparators and a second hypothesis of superiority was planned a priori if non-inferiority was proven. The results have been consistent in all three monotherapy pivotal trials. The IOP lowering efficacy of comparative treatments (timolol and latanoprost) has been in accordance to previous published results. Travoprost (0.0015% and 0.004%) dosed once daily produced both clinically relevant and statistically significant IOP reductions when used as a monotherapy. The IOP reductions were maintained over the entire 6 to 12 month treatment period.

The chosen non-inferiority margin is less than half the observed difference in change from baseline in IOP between timolol and placebo. In the view of the CPMP, in some circumstances a tighter margin may be appropriate but the chosen margin appears reasonable here. In any case the results indicate a satisfactory outcome even if a tighter margin were chosen. It is stated that if non-inferiority is being considered a per protocol analysis will be performed and if in fact superiority is found the analysis will be repeated using the ITT population. In the view of the CPMP, this approach is acceptable.

The CPMP raised a major objection regarding the absence of justification to accept the coexistence of the two different dosages due to the marginal difference of efficacy and safety between them. The

Applicant provided new analysis on efficacy and considered that travoprost 40 µg/ml would present the most favourable risk/benefit ratio over travoprost 15 µg/ml. The CPMP concluded that travoprost 0.0040% is numerically superior to travoprost 0.0015% in analyses on mean IOP efficacy. The rate of responders is superior with travoprost 0.0040%. The applicant has provided a new analysis of responders using more strict criteria that probably means that all patients included have really attained their target IOP that is supposed to stop further optic nerve damage. This analysis showed that 56.3% of patients were controlled with travoprost 0.004% when data were pooled over the three monotherapy studies whereas 49.8% were controlled with travoprost 0.0015%.

Additionally, in subgroup analyses of the studies, mean IOP reduction in black patients was up to 1.8mmHg greater than in non-black patients following treatment with 0.004% travoprost. It is not known at this time whether this difference is attributed to race or to heavily pigmented irides.

A second major objection was raised, as in the view of the CPMP, there was no justification to obtain a first line indication. Although a more potent effect on the decrease of IOP may be obtained with travoprost in comparison to timolol, the patients that need additional treatment based on their individual target IOP and the obtained effect may be identified in the follow up. In comparison to timolol, travoprost has, in general, worse ocular tolerability and a limited knowledge on its mechanism of action and on the long-term adverse effects. Efficacy and safety may be comparable to that of latanoprost, indicated in patients that do not tolerate or have insufficient response to any other treatment. The applicant agreed with the recommendation of the CPMP and the wording of the indication in the SPC was been modified to only include the second line.

The efficacy of travoprost 0.0015% and 0.004% as adjunctive therapy has been studied in one pivotal trial (C-97-73) where patients not adequately controlled with timolol have been randomised to add placebo, travoprost 0.0015% or travoprost 0.004% to timolol. As no comparison to another active treatment (e.g. latanoprost) in adjunctive therapy has been performed, there is information about the absolute efficacy of travoprost when added to timolol in patients not well controlled with timolol alone, but we do not know how it compares with other possible approved adjunctive therapies to timolol. When used adjunctively with timolol 0.5% BID, travoprost (0.0015% and 0.004%, dosed once daily) produced both clinically relevant and statistically superior IOP reductions compared to vehicle. The IOP reductions were maintained over the entire 6-month treatment period. The differences between travoprost 0.004% and 0.0015% were not statistically significant. The CPMP raised a third major objection regarding the limitations of the indication in adjunctive therapy (limited data with brimonidine, absence of data with other antiglaucomatous agents). This has been solved and the wording of the SPC has been modified in order to reflect these limitations.

Extension of indication to first line therapy

The application submitted for the extension of the indication to first line therapy included 4 Phase I studies, one Phase II study, one Phase III efficacy/safety study and 4 Phase IV post-marketing studies as well as interim analyses of the ongoing long term study C-99-10.

All these studies have been conducted according to applicable regulations on Good Clinical Practice.

Table. – 1 Clinical Studies completed since MAA submission

Phase of Study	Study Protocol Number
Phase I	C-00-05[a], C-00-15, C-00-56, C-00-11
Phase II	C-00-20[c]
Phase III	C-99-58[b]
Phase IV	C-00-57, C-01-24 [b], C-01-52, C-01-103 [b]

[a]Data for C-00-05 was submitted at Day 121 of the initial MAA approval process.
[b]Studies are considered completed once the database has been locked even if the final analysis and reporting is ongoing.
[C]Efficacy summary does not include C-00-20 since only the safety data has been analysed thus far.

Efficacy

Pharmacodynamic and pharmacokinetic studies

The new phase I pharmacodynamic studies (C-00-11, C-00-56) confirmed the IOP lowering effects of travoprost when it is administered to Japanese healthy volunteers. They confirm the results of previous dose-finding studies and provided additional short-term data on safety.

The pharmacokinetic study C-00-57 was submitted during the CPMP review process of the original Travatan MAA, and consequently, its results were taken into account and reflected in the SPC during the intial authorisation process. Study C-00-15 confirmed the known pharmacokinetic profile of travoprost and its active metabolite, and did not give rise to any changes to the SPC.

Clinical studies

The one phase II study submitted, C-00-20, is not included in the efficacy summary as only safety data has been analysed so far. One phase III short-term efficacy and safety study has been completed since the initial MAA (Study C-99-58) and is currently being analysed.

Four Phase IV post marketing studies, including one comfort study, two 24-hour dosing studies and one adjunctive therapy study, have been submitted (C-01-24, C-01-52, C-01-103 and C-00-57) of which the analyses are ongoing for two studies (C-01-24, C-01-103). Study C-01-52 was a safety study evaluating ocular comfort and hyperaemia.

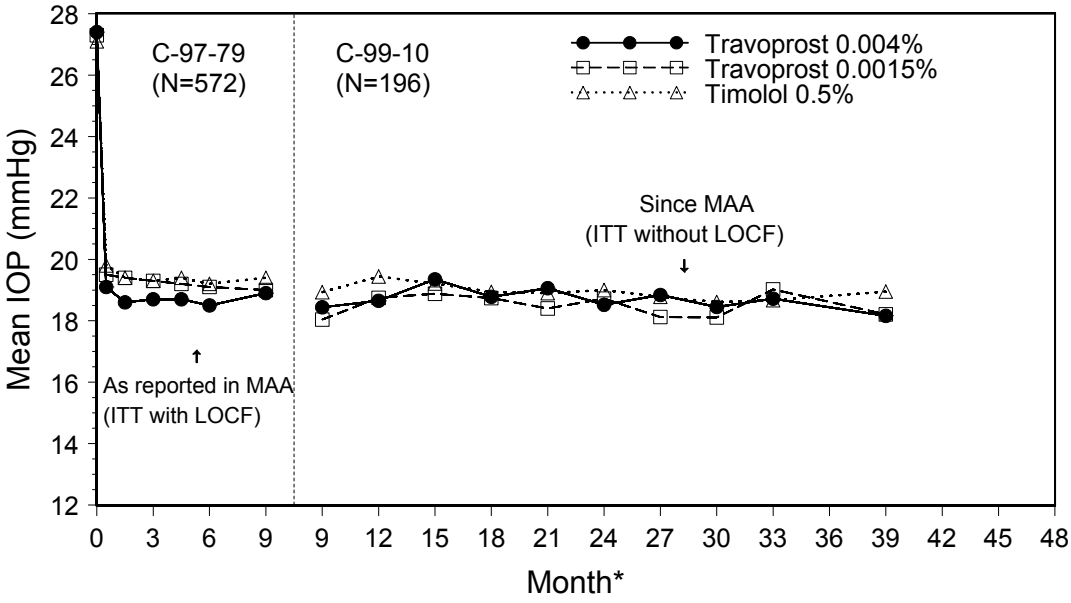
Study C-00-57 was a Phase IV efficacy and safety randomised trial of TRAVATAN dosed concomitantly to levobetaxolol hydrochloride 0.5% (BETAXON) or TRAVATAN alone in glaucoma or ocular hypertensive patients dosed for 10 weeks. There was a clinically relevant additional lowering of IOP (-2.2 to -2.7 mmHg) at 10 AM when BETAXON was dosed adjunctively once daily in the morning to TRAVATAN dosed once daily in the evening.

Regarding the ongoing efficacy studies, the most relevant for the present variation is the long-term study **C-99-10** that includes 139 patients that have been exposed for up to 4 years to travoprost.

The population participating in this study is those patients who successfully completed participation in clinical trial C-97-79 and who, in the opinion of the investigator, could continue with the same masked therapy. There was no interruption of therapy between participation in C-97-79 (which had a treatment duration of nine months, patients were treated with travoprost 0.0015%, travoprost 0.004% or timolol 0.5%) and C-99-10. Participation in study C-99-10 lasts for a total of 60 months with safety assessments performed quarterly for the first 2 years and semi-annually in the final 3 years. Although study C-99-10 was ongoing, an interim analysis of the data collected was submitted.

Descriptive statistics demonstrate that the IOP reductions produced by TRAVATAN at the initiation of the study were consistently maintained throughout the study (currently patients have been followed for up to 4 years).

C-97-79 and C-99-10
IOP at 9 AM



*In this ongoing study, up to July 2002, only 15 patients have reached the 45-month visit to provide data on this length of therapy. Thus data beyond 39 months is of limited value.

ITT = Intent-to-Treat; LOCF = Last-observation-carried-forward

Of the 196 patients initially enrolled in Study C-99-10, 67 were treated with TRAVATAN and 72 with travoprost 0.0015%. During the 4-year period, 12 patients withdrew from the trial, 6 due to adverse events, 5 requiring alternate therapy and 1 due to non-compliance. Therefore, 55/67 patients (82%) remain in the study in the TRAVATAN group (see the following table).

Duration of Exposure to Study Drug – C-99-10

Total Duration Across Time
(Safety Data)

		Months on Therapy													
	Total	10 to 12 Months		>12 to 18 Months		>18 to 24 Months		>24 to 30 Months		>30 to 36 Months		>36 to 42 Months		>42 to 48 Months	
Treatment	N	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Travoprost 0.0015%	72	72	100	70	97	66	92	64	89	60	83	55	76	7	10
Travoprost 0.004%	67	67	100	66	99	65	97	63	94	59	88	51	76	7	10
Timolol 0.5%	57	57	100	56	98	56	98	55	96	52	91	44	77	1	2

In the Request for Supplementary Information the CPMP queried whether bias may have been introduced as only patients continuing from study C-97-79 were recruited for the ongoing Study C-99-10.

In order to demonstrate that biases have not been introduced during the selection of those patients coming from study C-97-79 who participated in Study C-99-10, the MAH compared demographic, efficacy and safety profiles from different groups of patients. The main comparison was between patients who entered study C-99-10 (n=196) at the 31 sites that participated in this study vs. those patients who did not (n=135). Data have been also presented for the 28 sites that did not participate in C-99-10 (n=193) and for the overall intention-to-treat population (n=572).

Data presented show that the demographic characteristics of patients from the different subgroups were similar, with two non relevant exceptions, i.e. patients who completed C-97-79 and did not enter C-99-10 were older than those who did (15.2% vs. 4.5%, older than 75 years, respectively) and there

was a higher proportion of patients with pseudoexfoliation glaucoma amongst patients from centres that did not participate in study C-99-10.

Regarding efficacy, the IOP reductions were similar between the established groups.
From the safety point of view, there were no differences in the frequency and incidence of adverse events between patients who entered study C-99-10 and those who did not. Only a higher proportion of hypertension and cardiovascular disease was observed in those patients who were not enrolled in study C-99-10.

The CPMP concluded that these comparisons did not show any differences that would significantly bias in favour of patients entering the continuation study C-99-10.

In the Request for Supplementary Information the MAH was asked to comment on the IOP control in patients developing increased iris pigmentation.

The MAH presented mean and individual data for 9 patients, of which 2 already had increased iris pigmentation at study entry. The numbers of patients are clearly limited, but the CPMP agreed with the MAH that no adverse relationship between increased iris pigmentation and IOP is seen. This needs to be closely reviewed by the MAH particularly in the ongoing review of study C-02-20.

In the Request for Supplementary Information the CPMP pointed out that the risk of accumulation and release of pigment into the anterior chamber with a subsequent obstruction of the trabecular meshwork and additional increase in IOP might still be a concern that should be further studied. Limited data do not suggest that increased iris pigmentation is associated with any other symptoms, and the MAH will conduct a trabecular meshwork study including an evaluation of the effects of travoprost treatment on patients with iris colour changes (C-01-78). Therefore, the MAH was asked to confirm that this study and other studies that address this issue are designed to provide information to 1) exclude any correlation between increased iris pigmentation and anterior chamber pigmentation, and 2) exclude a correlation with anterior chamber pigmentation and increased IOP.

In the response the MAH confirmed the intention of conducting a clinical study (C-01-78) which will evaluate the pigmentation of trabecular meshwork in 30 subjects after 2 years of treatment of TRAVATAN compared to 30 subjects with no prior exposure to a prostaglandin analogue, and who are in need of trabeculectomy. The MAH argued that although the study may include patients who present with an iris pigmentation change, the study is not targeted to exclude a possible correlation between increased iris pigmentation, anterior chamber pigmentation and IOP.

The MAH is conducting two long-term safety studies, C-02-20 and C-99-10, and proposed to monitor the trabecular meshwork pigmentation of the patients enrolled in both studies, using gonioscopy. This information collected in C-02-20, i.e., in patients who will likely not present iris pigmentation at study start, will assess the incidence of this effect and of trabecular meshwork pigmentation in a glaucoma population. Furthermore, the same information collected in C-99-10 (from Visit Month 48 onwards) will assess the correlation between iris pigmentation and trabecular pigmentation, in addition to monitoring the IOP over five years of treatment. This proposal was acceptable to the CPMP.

The CPMP also requested that the MAH should further discuss the extent of efficacy and safety data in patients with a wider range of glaucoma aetiologies, and in combination with a wider range of glaucoma medication in view of the proposed first line indication.
The MAH responded that there was a small number of patients with pigmentary glaucoma or pseudoexfoliative glaucoma in the original Phase III studies, where there were no clear differences with regard to IOP control or adverse events noted compared to other patients. This is supported by review of the post marketing surveillance. There is an ongoing study in chronic angle-closure glaucoma (C-01-38) and the MAH proposed to submit the results of this study to the CPMP. This proposal was acceptable to the CPMP.

In addition to the previously submitted data on combination treatment with timolol, levobetaxolol and brimonidine, a study involving combination with the topical carbonic anhydrase inhibitor brinzolamide is to be initiated. The MAH proposed to submit the protocol for this study to the CPMP for review, which was considered acceptable to the CPMP.

The MAH was also asked in the Request for Supplementary Information to provide a proposal how further to study the safety and efficacy of TRAVATAN in the first line treatment of raised intraocular

pressure. The MAH proposed to provide the CPMP with safety reports annually of each of the four studies of TRAVATAN that are currently ongoing or planned. This is acceptable to the CPMP.

The MAH has proposed to investigate the possibility to undertake the follow up of about 2000 patients in the United Kingdom under the Prescription Event Monitoring (PEM) Scheme. This follow up procedure would start once TRAVATAN is approved with a first-line indication. The MAH proposed to submit the protocol to the CPMP for review, which was considered acceptable to the CPMP.

Clinical safety

Patient exposure

A total of 2,927 patients or subjects were included in the safety analysis of the ten completed phase I-III travoprost studies. Of these, 2881 patients participated in phase II and III studies and 46 participated in phase I studies.
One thousand nine hundred and twenty-five (1925) subjects/patients have been exposed to Travoprost to date in ten clinical studies. The combined number of subjects/patients evaluated for safety with Travoprost 0.0015% and Travoprost 0.004% in monotherapy was 1,367. Duration of exposure ranged from 1 to 365 days with Travoprost 0.0015% (mean exposure: 233.0 days; median: 259.0 days) and from 1 to 470 days with Travoprost 0.0040% (mean exposure: 210.9 days; median: 194.0 days).. The safety of Travoprost 0.0015% was evaluated in 657 subjects/patients (ages 18 to 88 years), and the safety of Travoprost 0.004% was evaluated in 710 subjects/patients (ages 20 to 94 years).

The mean age of the patients included in pivotal trials was 63.8 years (47% up to 65 years and 53% over the 65). Both male and female (with the exception of women of childbearing potential) were allowed in the studies. Other demographic data collected in the studies included the iris colour and the etiology of increased IOP (ocular hypertension, open-angle glaucoma, pigmentary glaucoma and pseudoexfoliation glaucoma. Patients with IOP higher than 36 mmHg were excluded.

Travoprost concentrations used in the complete clinical trials ranged from Travoprost 0.0001% to 0.006% (1 to 60 µg/ml) and the dosing regimen was one drop once a day (preferably in the evening). Only one study (C-99-18) assessed the BID dosing regimen during 6 weeks (C-99-18)in 32 adult patients (ages 32 to 75 years) with open-angle glaucoma, ocular hypertension, or pigmentary glaucoma.

Adverse events and serious adverse events/deaths

No serious adverse events related to Travoprost 15 or 40 µg/ml were reported during the studies. Adverse events related to Travoprost 15 or 40 µg/ml were generally mild to moderate, usually resolved with or without treatment, and generally did not interrupt continuation in the study.

Ocular adverse events related to travoprost
The most common ocular adverse events related to Travoprost 15 or 40 µg/ml were ocular hyperaemia, ocular discomfort (burning, stinging), and ocular pruritus.

Systemic adverse events related to travoprost

In the monotherapy studies, 26 of the 657 patients (4.0%) experienced 29 systemic events related to Travoprost 15 µg/ml, and 26 of the 710 patients (4.1%) experienced 34 systemic events related to Travoprost 40 µg/ml.

The most frequent systemic events associated with Travoprost 15 µg/ml were headache (0.8%), asthenia (0.3%), hypotension (0.3%), myalgia (0.3%), rhinitis (0.3%), erythema (0.3%), and pruritus (0.3%). The most frequent systemic events associated with Travoprost 40 µg/ml were headache (1.4%), skin discolouration (0.6%), hypotension (0.3%), and bradycardia (0.3%). In comparison, the most frequent systemic events related to Latanoprost 0.005% were hypotension (0.5%), arthritis (0.5%), and taste perversion (0.5%). There were no reports of systemic events related to Placebo.

Numerous concomitant medications were used during the studies. Few drug interactions were noted for patients receiving Travoprost 15 or 40 µg/ml. One patient receiving Travoprost 15 µg/ml

experienced conjunctivitis and ocular hyperaemia related to a possible drug interaction with sodium cromoglycate and ketorolac. Another patient receiving Travoprost 40 µg/ml experienced blurred vision related to a possible drug interaction with naproxen. A third patient receiving Travoprost 40 µg/ml experienced dry eye and ocular pruritus related to an unspecified possible drug interaction.

Serious Adverse Events

Serious Ocular Events Related to Therapy
No serious ocular events related to Travoprost Eye Drops were reported. Severe ocular pain and ocular hyperaemia related to Travoprost 15 µg/ml was reported in one of the 657 patients (0.2%), and ocular pain and ocular discomfort related to Travoprost 40 µg/ml were reported in two of the 710 patients (0.3%). In the monotherapy studies with Travoprost 15 µg/ml, 10 of the 657 patients (1.5%) were discontinued due to ocular events (hyperaemia, discomfort, pain, pruritus, cells, conjunctival follicles, eye disorder [corneal pigment stippling], ocular fatigue, and/or conjunctivitis) related to therapy . In the monotherapy studies with Travoprost 40 µg/ml, 30 of the 710 patients (4.2%) were discontinued due to ocular events (hyperaemia, discomfort, pain, pruritus, flare, cells, foreign body sensation, conjunctivitis, hair disorder [increased eyelash length], browache, and/or dry eye) related to therapy. Ocular hyperaemia and ocular discomfort were the most frequent reasons for discontinuation of patients with treatment-related ocular events.

Serious Systemic Events Related to Therapy
No deaths or other serious events related to Travoprost 15 or 40 µg/ml were reported during the studies. One patient receiving Travoprost 15 µg/ml and Timolol 0.5% experienced a serious lung disorder (chronic obstructive pulmonary disease) related to Timolol 0.5%. No severe systemic event was related to Travoprost Eye Drops. Four of the 657 patients (0.6%) discontinued due to headache, asthenia, abdominal pain, decreased libido, rhinitis, erythema and/or pruritus related to Travoprost 15 µg/ml (See Part IV). Six of the 710 patients (0.8%) discontinued due to headache, asthenia, malaise, hypotension, cardiac arrhythmia, skin discolouration and/or contact dermatitis related to Travoprost 40 µg/ml.

Serious events unrelated to travoprost
One hundred serious events unrelated to Travoprost 15 or 40 µg/ml were reported. Seventy-two patients receiving Travoprost 15 or 40 µg/ml discontinued from the study due to adverse events; 45 patients discontinued due to treatment-related adverse events and 27 patients were discontinued due to treatment-unrelated adverse events. Six patients receiving Travoprost 15 or 40 µg/ml experienced fatal treatment-unrelated adverse events secondary to intercurrent illness

No other serious events related to Travoprost 15 or 40 µg/ml were reported during the studies. In the monotherapy studies, 101 serious events unrelated to Travoprost 15 or 40 µg/ml were reported in 67 patients. In the adjunctive therapy studies, one serious expected event (lung disorder – exacerbation of chronic obstructive pulmonary disease) related to Timolol 0.5% was reported in a patient receiving Travoprost 15 µg/ml with Timolol 0.5%. In the adjunctive therapy studies, fifteen additional serious events unrelated to Travoprost 15 or 40 µg/ml were reported in nine patients.

<u>Discontinuations due to adverse events</u>

Seventy-two of the 1367 patients (5.3%) were discontinued from the studies due to adverse events related or unrelated to Travoprost 15 or 40 µg/ml in monotherapy studies. Forty-five of the 1367 patients (3.3%) receiving Travoprost 15 or 40 µg/ml discontinued from the studies due to non-serious treatment-related adverse events. Fifteen of the 1367 patients (1.1%) receiving Travoprost 15 or 40 µg/ml discontinued from the studies due to serious treatment-unrelated adverse events. Twelve of the 1367 patients (0.9%) receiving Travoprost 15 or 40 µg/ml discontinued from the studies due to non-serious treatment-unrelated adverse events.

Thirty-one of the 657 patients (4.7%) receiving Travoprost 15 µg/ml discontinued from the studies due to treatment-related and -unrelated adverse events. Forty-one of the 710 patients (5.8%) receiving

Travoprost 40 µg/ml discontinued from the studies due to treatment-related and -unrelated adverse events. For comparison, six of the 196 patients (3.1%) receiving Latanoprost 0.005% discontinued due to treatment-related and -unrelated adverse events. Twenty-eight of the 727 patients (3.9%) receiving Timolol 0.5% discontinued from the studies due to treatment-related and -unrelated adverse events.

For patients receiving Travoprost 15 or 40 µg/ml, the most frequent reason for discontinuation of patients with treatment-related adverse events was ocular hyperaemia.

Laboratory findings

Blood chemistry, haematology and urinalysis values were measured in two studies. No clinically significant changes from baseline within treatment groups were observed. There was no evidence of Travoprost Eye Drops having any clinically relevant effect on laboratory data.

Special safety issues

Visual Acuity
No clinically significant difference in visual acuity change from baseline was observed between Travoprost Eye Drops and Latanoprost 0.005% or Timolol 0.5%.

Ocular Signs
Ocular signs (cornea, iris/anterior chamber, lens, vitreous) were observed at Screening, Eligibility 2 (baseline) and all subsequent visits in eight clinical studies (Protocols C-96-52, C-97-02, C-97-71, C-97-72, C-97-73, C-97-79, C-98-09, C-99-18). Any clinically significant increase of one or more units from baseline in ocular signs was identified and reported as an adverse event.

In the monotherapy studies, clinically significant increase in ocular signs was noted in 33 of the 643 evaluated patients (5.1%) receiving Travoprost 15 µg/ml and 40 of the 676 evaluated patients (5.9%) receiving Travoprost 40 µg/ml. In the adjunctive therapy studies, eight of the 139 patients (5.8%) receiving Travoprost 15 µg/ml with Timolol 0.5% and six of the 143 patients (4.2%) receiving Travoprost 40 µg/ml with Timolol 0.5% experienced clinically significant increase in ocular signs. In comparison, 11 of the 196 patients (5.6%) receiving Latanoprost 0.005% and 38 of the 723 patients (5.3%) receiving Timolol 0.5% experienced clinically significant increase in ocular signs.

Dilated Fundus
Dilated fundus examination (retina/macula/choroid, optic nerve, disc pallor) was performed at Screening (baseline), final, and unscheduled visits (if warranted) in seven clinical studies (Protocols C-96-52, C-97-71, C-97-72, C-97-73, C-97-79, C-98-09, C-99-18). In one clinical study (C-96-52), dilated fundus at the final visit was collected only at one selected clinical investigator site. Any clinically significant increase of one or more units from baseline in dilated fundus parameters at the final visit was reported as an adverse event. No clinically significant difference in fundus parameters was observed between Travoprost 15 or 40 µg/ml and other treatment groups.

Visual Fields
Automated perimetry was collected for safety evaluation, no clinically relevant changes from baseline were observed in patients receiving Travoprost Eye Drops and other treatments. Analysis of visual fields showed that no clinically relevant deterioration from baseline in mean deviation, corrected pattern standard deviation, mean defect, or corrected loss variance was observed in any treatment group.

Cells and Flare
Assessment of aqueous flare and/or inflammatory cells was performed at Eligibility 2 (baseline) and all subsequent visits in seven clinical studies (Protocols C-96-52, C-97-02, C-97-71, C-97-72, C-97-73, C-97-79, C-98-09). Clinically significant increase of one or more units from baseline in aqueous flare or inflammatory cells was reported as an adverse event. In the monotherapy studies, two of the 657 patients (0.3%) receiving Travoprost 15 µg/ml and three of the 710 patients (0.4%) receiving Travoprost 40 µg/ml discontinued due to cells and/or flare. In the adjunctive therapy studies, one of the 142 patients (0.7%) receiving Travoprost 15 µg/ml with Timolol 0.5% and two of the 145 patients

(1.4%) receiving Travoprost 40 µg/ml with Timolol 0.5% discontinued due to cells and/or flare. In comparison, none of the 196 patients receiving Latanoprost 0.005% discontinued due to cells and/or flare, and two of the 727 patients (0.3%) receiving Timolol 0.5% discontinued due to cells and/or flare.

In the monotherapy studies, five of the 595 evaluated patients (0.8%) receiving Travoprost 15 µg/ml and 11 of the 676 evaluated patients (1.6%) receiving Travoprost 40 µg/ml experienced a clinically significant increase from baseline in aqueous flare. In the adjunctive therapy studies, five of the 139 patients (3.6%) receiving Travoprost 15 µg/ml with Timolol 0.5% and two of the 143 patients (1.4%) receiving Travoprost 40 µg/ml with Timolol 0.5% experienced a clinically significant increase in aqueous flare. In comparison, two of the 196 patients (1.0%) receiving Latanoprost 0.005% and four of the 723 patients (0.6%) receiving Timolol 0.5% experienced clinically significant increase in aqueous flare.

In the monotherapy studies, eight of the 595 evaluated patients (1.3%) receiving Travoprost 15 µg/ml and ten of the 628 evaluated patients (1.6%) receiving Travoprost 40 µg/ml experienced a clinically significant increase from baseline in inflammatory cells. In the adjunctive therapy studies, eight of the 139 patients (5.8%) receiving Travoprost 15 µg/ml with Timolol 0.5% and six of the 143 patients (4.2%) receiving Travoprost 40 µg/ml with Timolol 0.5% experienced a clinically significant increase in inflammatory cells. In comparison, one of the 196 patients (0.5%) receiving Latanoprost 0.005% and nine of the 723 patients (1.2%) receiving Timolol 0.5% experienced clinically significant increase in inflammatory cells.

Corneal Health Assessment
Clinical Study C-97-71 included a 12-month evaluation of Travoprost Eye Drops on corneal health by assessing corneal thickness and endothelial cell density. No clinically relevant or statistically significant mean change from baseline in corneal thickness or endothelial cell density was observed between Travoprost Eye Drops, Timolol 0.5% and Latanoprost 0.005%.

Pulse and Blood Pressure
No treatment related cardiovascular events relevant to blood pressure or pulse were reported for Travoprost Eye Drops.

Iris Pigmentation
Iris pigmentation change was observed in approximately 2 to 3% of patients receiving Travoprost 15 or 40 µg/ml compared to approximately 5% of patients receiving Latanoprost 0.005%. This unique side effect is based on the ability of prostaglandin analogues to stimulate melanin formation in melanocytes. For latanoprost, it has been reported that it is possible that this agent only selectively stimulates the iridal melanocytes from mixed coloured irides. Stimulation of melanogenesis of iridal melanocytes may not be a general response. No increased proliferation of normal dermal and uveal melanocytes has been observed. It is unknown whether this darkening is reversible upon discontinuation of a prostaglandin analogue.

Eyelashes
Hypertrichosis has been reported in the literature with topical prostaglandin analogues and was therefore also evaluated specifically by the Applicant. The assessment was performed by independent and masked readers using the same photographs as for the evaluation of iris colour changes. The evaluation indicated that 839 of the 2,391 patients (35.1%) receiving Travoprost Eye Drops, Timolol 0.5% or Latanoprost 0.005% in monotherapy or adjunctive therapy studies experienced eyelash changes over the course of the studies.

The majority of the eyelash changes associated with Travoprost Eye Drops included changes in colour, length, density and/or thickness. A concentration-related change was observed between patients receiving Travoprost 15 µg/ml (48.1%) and 40 µg/ml (59.2%). Patients receiving Latanoprost 0.005% also experienced similar changes (25.8%). This is a common cosmetic effect observed with this class of compounds and did not appear to pose any safety issues to the patient or interfere with daily activity.

Macular disorder

Cystoid macular oedema (CME) has also been reported during treatment with ophthalmic prostaglandin $F_{2\alpha}$ analogues and is currently included in the SPC for Latanoprost.No reports of CME in any patient treated with Travoprost 15 or 40 µg/ml have occurred. Even though there were no reports of CME in the Travoprost clinical trials, it should be noted that many of the risk factors for CME were exclusion criteria in the studies.

Safety in special populations

Renal impairment
One study has been performed in subjects with normal and impaired renal function. In study (C-99-97) following multiple topical ocular doses of travoprost 40 µg/ml (one drop in each eye once in the morning) for 7 days, plasma and urine samples for travoprost and AL-5848 (the free acid) determinations were collected after the morning dose on Days 1 and 7. Plasma concentrations of AL-5848 could not be correlated with creatinine clearance. Regarding safety, no serious adverse events related to or unrelated to travoprost were reported during the study. There were no clinically significant mean changes from baseline in laboratory data observed in subjects receiving Travoprost 40 µg/ml. There were no clinically significant mean changes from baseline in pulse, systolic blood pressure or diastolic blood pressure. Travoprost was safe and well tolerated in subjects with renal impairment. There seems to be no necessity of adjustment of dose in renal impaired patients.

Hepatic impairment
Steady state pharmacokinetics of travoprost in subjects with normal and impaired hepatic function has been evaluated following multiple topical ocular doses in study C-00-05. No serious adverse events related to or unrelated to travoprost were reported during the study. There were no clinically significant mean changes from baseline in laboratory data observed in subjects receiving Travoprost 40 µg/ml. There were no clinically significant mean changes from baseline in pulse, systolic blood pressure or diastolic blood pressure. Travoprost was safe and well tolerated in adult subjects with normal or impaired hepatic function. There seems to be no necessity of adjustment of dose in patients with impaired hepatic function.

Pregnant and potential childbearing Women
No studies with travoprost including pregnant or potential childbearing women have been performed and pregnancy was one of the exclusion criteria. Travoprost Eye Drops has potential hazardous pharmacological effects, with respect to the course of pregnancy, to the unborn and neonate. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate of resorption observed in pregnant rats and mice at doses at or above 1 µg/kg/day. Therefore, Travoprost Eye Drops should not be used during pregnancy**.** Travoprost and its metabolites may pass into breast milk and Travoprost Eye Drops should therefore not be used in nursing women or breast-feeding should be stopped.

A statement that travoprost should not be used during pregnancy, unless clearly necessary, and must not be used in women attempting pregnancy has been included in the SPC.

Children
Travoprost has not been assessed in patients under 18 years of age. In line with to the absence of data in pediatric population, a statement not recommending the use of travoprost in patients under 18 years of age has been included in section 4.2 of SPC. Although from the available evidence this is correct, in the view of the CPMP, the issue relative to the product safety and efficacy in children should be further addressed by the applicant.

Post marketing experience

Iris colour changes

In December 2001, the MAH submitted the first annual update on all patients that were treated with travoprost during the controlled clinical studies, and who experienced iris colour changes in the two studies (C-97-77 and C-99-10), which were both ongoing.

Study C-97-77 is a two-year follow-up safety study of patients with iris pigmentation changes resulting from participation in Travoprost (AL-6221) Phase III Clinical Trials C-97-71, C-97-72, C-97-73, C-97-79 and C-99-10.

A total of 35 patients who experienced changes in iris colour entered C-97-77. Ten of them were treated with travoprost 0.004%, fifteen with travoprost 0.0015% and ten with latanoprost 0.005% prior to entering C-97-77. Currently 24 patients have completed the 2 year follow-up, 8 are still ongoing and 3 patients dropped out.

Ten patients have been treated with travoprost 0.004%, latanoprost 0.005% and/or isopropyl unoprostone for a period of time during their participation in C-97-77.
The iris colour did not change during the 2-years follow-up in any of patients suggesting that the iris colour changes seem to be permanent.

Study C-99-10 included patients who had successfully completed C-97-79 (9-month comparison of travoprost (0.0015% and 0.004%) and timolol 0.5%) and by enrollment the patients were invited to continue treatment for up to 5 years.

Out of the 573 patients randomised to Protocol C-97-79, 196 rolled-over into this extension study C-99-10. Twelve patients with iris colour changes are being followed in the extension study C-99-10. Two patients with iris colour changes experienced an increase in lens scores.

Only one spontaneous report of iris discolouration had been received. This was a consumer report and no further details regarding treatment duration were available.

Based on this first annual update the CPMP concluded that the iris colour changes induced by travoprost are permanent and requested the MAH to amend the Product Information accordingly, which the MAH did through a Type II variation.

Macular oedema, asthma, asthma exacerbation and abnormal hair growth on eyelids.

Nine cases of macular oedema have been reported since the international birthdate, 5 of them during the reporting period of the second PSUR (covering the period from 1 May 2002 to 31 October 2002). Considering the number of cases reported and the fact that macular oedema had also been reported with other drugs of the same therapeutic class, the CPMP requested this reaction to be added to section 4.8 of the SPC.

During the reporting period for the second PSUR, 3 cases of hair growth abnormal and one case of hypertrichosis were reported. The CPMP therefore requested that the term "abnormal hair growth on eyelids" was added to the section 4.8 of the SPC and reflected in the Package Leaflet.

Three cases of asthma aggravated and 1 case of asthma were reported in the second PSUR. Since the international birthdate 3 cases of asthma aggravated and 2 of asthma have been reported. Rare cases of asthma, asthma exacerbation and dyspnoea have been reported with other prostaglandin $F_2\alpha$ analogue. The CPMP therefore requested following the assessment of the second PSUR that asthma and asthma exacerbation should be added to section 4.8 of the SPC. These terms were also added to the Package Leaflet.

Discussion on Clinical Safety

The extent of exposure to travoprost monotherapy during the clinical development plan seems acceptable and includes 657 patients exposed to 0.0015% (mean time of exposure 233 days) and 710 to 0.004% (mean time of exposure 211 days). The proportion of patients experiencing any related adverse event was about 40% of those patients receiving Travoprost 0.0015% and about 50% of those receiving Travoprost 0.004%. Most of adverse events were mild and non-serious and 5.3% of the

patients treated with travoprost 0.0015% and 6.2% of the of the patients treated with travoprost 0.0040% discontinued treatment due to any adverse event, related or unrelated to the therapy.

Most related adverse reactions were ocular, mainly hyperemia, (27.4% for travoprost 0.015%, 37.3% for travoprost 0.004% and 24.0% for latanoprost) burning or stinging, pruritus, iris discolouration and others. With regard to related systemic adverse reactions, they appeared in about 4% of patients The most frequently reported reaction was headache (1.4%). No deaths or other serious events related to Travoprost 15 or 40 μg/ml were reported during the studies. No treatment-related changes in biochemical or haematological parameters have been found

Ocular side effects were comparable to those described with latanoprost. Travoprost has been compared to latanoprost in one study in monotherapy. The frequency of related ocular hyperaemia was 46.0% for travoprost 0.0040% and 24.0% for latanoprost and the frequency of iris discolouration was 3.0% for travoprost 0.0040% and 5.1% for latanoprost. Overall, in the view of the CPMP the tolerability of travoprost is not inferior to latanoprost. In comparison to timolol, the frequency of ocular side effects is higher with travoprost than with timolol. On the other hand, less systemic cardiovascular and respiratory effects could be expected although this has not been evidenced in the submitted clinical trials.

The CPMP requested that a sentence about glaucomas or ocular hypertension superior to 36 mmHg should be included in the SPC, stating that there is no available data on these cases. Regarding iris pigmentation, it was also requested by the CPMP that the statement: ”It is unknown whether this darkening is reversible upon discontinuation of a prostaglandin analogue” should be included in the SPC.

Travoprost 0.0040% has an acceptable safety profile. The most frequent adverse ocular event related to both concentrations has been hyperaemia. The frequency and incidence of hyperaemia and discontinuation rate due to hyperaemia with travoprost 0.0040% was superior to travoprost 0.0015% and the severity of hyperaemia in the travoprost 0.0040% group was also superior. However, it should be recognised that hyperaemia has, from a clinical point of view, a limited relevance and that this incremental incidence of hyperaemia may be considered as counterbalanced by the higher efficacy obtained.

Safety data for the extension of indication to first line therapy

The Safety Update for TRAVATAN submitted in the application for first line indication included new safety data from 10 studies that have been completed since the MAA was submitted in November 2000. Furthermore, adverse event experience in the clinical trials initially included in the MAA and post-marketing data were presented.

The major concerns regarding prostaglandin analogues as first line therapy were the adverse events such as iris colour changes, eyelash changes, periocular skin changes and cystoid macular oedema (CME). Data on these adverse events were therefore also included in the safety update as well as long-term safety data (C-99-10).

Patients exposure

The additional 10 clinical studies completed since the MAA included an overall total of 786 patients (including 86 from C-00-20) of which 263 patients (including 21 from C-00-20) were exposed to TRAVATAN as monotherapy. The overall exposure for TRAVATAN monotherapy in completed clinical studies as of September 2002 included 973 patients as presented in the following table. This table also includes exposure information as a reference point based upon the previous MAA submission.

Exposure to Travoprost 0.004% in Completed Clinical Studies

Document (Submission Date)	Completed Clinical Studies (No. of patients)	Patients Exposed to Travoprost 0.004%*
MAA (November 2000)	10 (2,922)	710**
First line indicaiton Variation (November 2002)	20 (3,622)	973***

*Cumulative exposure to Travoprost as monotherapy in completed clinical studies, including C-00-20. C-00-20 is not included in the efficacy or exposure section as efficacy or exposure data analysis is ongoing.
**Two patients were evaluated for safety but information on exact length of exposure is missing.
***Includes 20 patients from C-00-20 not included in efficacy or exposure summary as only the safety data has been analysed and efficacy and exposure data analysis is ongoing.

When the MAA was submitted, a total of 655 patients had been exposed to travoprost 15 μg/ml in monotherapy (292 for more than 9 months) and 708 patients had been exposed to TRAVATAN (travoprost 40 μg/ml), of which 271 patients had been treated for 9 months or more. Other concentrations of travoprost and combinations with other anti-glaucoma medications were tested in short-term studies, adding up to 1,921 patients that had been exposed to the drug.

In the first line indication variation application 569 additional patients were included who have completed treatment with travoprost in short-term clinical trials and 139 who had entered in the long-term study, C-99-10. Out of the total of 708 travoprost treated patients, 460 were exposed to TRAVATAN of which 67 patients were enrolled in C-99-10.

In total, 3,622 patients encompassing all treatments studied were included in the analysis. Of these, 2,922 were described in the original MAA. A total of 896 patients are providing new data, however, this includes 196 patients who rolled over into study C-99-10 (new since the original MAA) from study C-97-79 (included in the original MAA).

The details regarding exposure of patients in the long-term study C-99-10 are presented in the section on efficacy.

Adverse events

Overall, in the additional 10 studies (C-00-05, C-00-15, C-00-56, C-00-11, C-00-20, C-99-58, C-01-24, C-01-52, C-01-103, C-00-57)(N=263) no deaths or other serious adverse events were reported. The types of adverse events observed during these studies were similar to those reported in the MAA. No serious, unexpected, related adverse events have been reported in the additional completed clinical studies. The most common ocular adverse events (related and not-related combined) reported were ocular hyperaemia (36.1%), ocular pruritus (4.9%), dry eye (3.8%), ocular pain (3.4%) and photophobia (2.7%). The most common systemic adverse event was headache (1.9%), with all other systemic adverse events occurring at an incidence of 0.8% (2/263) or less.

Ocular adverse events related to TRAVATAN monotherapy in the additional 10 studies that were most common were ocular hyperaemia (36.1%), ocular pruritus (4.6%), ocular discomfort (3.0%), ocular pain (2.7%) and photophobia (2.3%). Headache (0.8%) was the most common systemic adverse event reported as related to TRAVATAN monotherapy, with all other systemic related adverse events occurring at an incidence of 0.4% (1/263).

Adverse events for ocular hyperaemia, ocular pruritus, dry eye, ocular pain, and photophobia were generally mild and did not require adjunctive treatment. Ocular hyperaemia, ocular pruritus, dry eye, ocular pain, and photophobia were generally related to treatment and are included in the SPC for TRAVATAN. There were no new ocular adverse events reported that had not previously been reported (as either related or not-related) for travoprost 0.004% monotherapy or as adjunctive therapy in the MAA submission.

The most common systemic adverse event (related and not related combined) reported in the additional ten studies was headache (1.9%). The systemic adverse events reported in the ten additional studies were similar in type to those reported in the MAA.

Two new systemic adverse events (maculopapular rash and skin disorder) were reported, once each, in the ten newly completed studies that had not been reported previously in clinical studies with travoprost. Both of these resolved and were considered not-related to study medication. Facial oedema, arthralgia, systemic pruritus, and urticaria have not been reported with travoprost 0.004% previously, but have been reported with travoprost 0.0015% in earlier studies. These adverse events were considered not-related to study drug.

No clinically relevant difference in safety was observed in the 10 additional completed studies when compared with the MAA clinical study database. This was based upon an assessment of reported adverse events, and other safety parameters (see table below).

The other safety parameters included in one or more of the ten recently completed studies were visual acuity, ocular signs and symptoms (slit-lamp and fundus examinations), cardiovascular parameters (pulse and blood pressure), ocular hyperaemia, iris and eyelash photographs, pupil diameter, laboratory parameters (haematology, blood chemistry and urinalysis), visual field and physical examination. These other safety assessments did not identify any new safety issues for TRAVATAN. No clinically relevant treatment-related changes in laboratory parameters were observed during these studies.

The most common ocular adverse events (related and not-related combined) reported in the combined MAA and additional 10 studies include ocular hyperaemia (39.4%), ocular pruritus (6.6%), ocular pain (5.0%), and ocular discomfort (4.8%). The most common systemic adverse events (related and not-related combined) include headache (3.1%), hypertension (3.0%), infection (2.6%), and flu syndrome (2.0%). These adverse events are consistent with those reported in the MAA for TRAVATAN.

Ocular adverse events related to TRAVATAN monotherapy in the combined MAA and additional 10 studies that were most common were ocular hyperaemia (37.0%), ocular pruritus (5.3%), ocular discomfort (4.0%), and ocular pain (3.3%). Headache (1.2%) was the most common systemic adverse event reported as related to TRAVATAN monotherapy, with all other systemic related adverse events occurring at an incidence of 0.5% (5/973) or less. Overall, no deaths or other serious adverse events related to therapy were reported.

Long-Term Safety Data

An interim safety analysis has been done for study C-99-10 in order to provide long-term safety data to support a first-line indication for TRAVATAN.

Regarding deaths, three patient deaths were reported which included two in the travoprost 0.0015% group (pulmonary emboli and carcinoma) and one in the travoprost 0.004% group (lung carcinoma) and all were unrelated to the study drug. All serious adverse events reported to date have been assessed as not-related to the use of study medication.

The most frequent adverse event assessed to be related to study drug is ocular hyperaemia occurring at an incidence of 13.9% in the travoprost 0.0015% group, an incidence of 23.9% in the travoprost 0.004% group, and an incidence of 3.5% in the timolol 0.5% group. Other treatment related ocular adverse events reported with travoprost 0.004% included iris discolouration (9.0%), ocular pain (6.0%), ocular discomfort (4.5%), ocular pruritus (3.0%), dry eye (1.5%), foreign body sensation (1.5%), increased IOP (1.5%), and ocular irritation (1.5%).

Four patients discontinued due to treatment related adverse events, which included three in the travoprost 0.004% group (ocular discomfort, ocular dryness, ocular hyperaemia and ocular pain) and one in the timolol 0.5% group (dyspnoea).

Iris pigmentation changes

Change of iris colour is based on the ability of prostaglandin analogues to stimulate melanin formation in melanocytes. The exact mechanism of action is still being elucidated but current studies suggest that natural prostaglandins (such as $PGF2_{\alpha}$) as well as some prostaglandin analogues enhance the activity of tyrosinase, an enzyme that up-regulates an aminoacid essential in the pathway of melanogenesis. Melanogenesis may also be mediated through an increase of endogenous PGE2. However, although this increased pigmentation is not resulting from increased cell division, it is generally not reversible,

and is considered a safety concern. Iris colour change resulting from increased melanogenesis can be classified as a class effect of prostaglandin analogues.

Iris pigmentation changes have been reported in subjects treated with TRAVATAN. In the MAA, there were 15 subjects (2.1%) from the TRAVATAN 0.0040% treatment group and 20 subjects (2.5%) from the TRAVATAN 0.0015% treatment group reported to have had iris pigmentation changes.
Two studies have been completed since the MAA filing that collected information on iris pigmentation changes (C-00-11 and C-99-58). These studies have no shown changes in iris pigmentation.

Although iris colour photographs were taken in 7 of the studies included in the MAA and one completed study since the MAA (Study C-00-11), iris colour changes have only been noted in the longer-term studies (6 months duration or more).

To further evaluate iris pigmentation changes, two ongoing studies (C-97-77 and C-99-10) are following subjects for up to five years. Study C-97-77 enrolled 35 subjects with a documented iris pigmentation change from a previous MAH sponsored clinical trial, while C-99-10 includes 196 subjects on randomised treatment with travoprost 0.0015%, travoprost 0.0040% or timolol 0.5% for up to five years.

The ongoing C-99-10 long-term study is collecting iris colour photographs, and iris pigmentation changes have been seen in this study as well. Currently, 5 of the 196 (6.9%) subjects treated with travoprost 0.0015% and 6 of 196 (9%) subjects treated with travoprost 0.0040% have adverse events reported for iris pigmentation change in this ongoing study.

Iris pigmentation changes have been seen in a total of 21 patients on TRAVATAN as monotherapy or as adjunctive therapy, with on-therapy patient follow-up extending up to 4 years. When examining the time-course of the patients with iris pigmentation changes in these studies with a minimum duration of 6 months (C-97-71, C-97-72, C-97-79, C-97-73 and C-99-10), most of these changes (16 of 21) occurred within one year of therapy. The remaining 5 cases were reported between one and 2 years of therapy. To date, no additional iris colour changes have been reported after 2 years of therapy.

Time Scale for Iris Colour Changes

	CUMULATIVE FREQUENCY OF IRIS COLOUR CHANGES		
Months on Therapy	**TRAVATAN Total Number***	**TRAVATAN (C-97-71)****	**XALATAN (C-97-71)*****
3	2	1	1
6	9	3	5
9	13	5	6
12	16	6	10
15	19	--	--
18	20	--	--
21	20	--	--
24	21	--	--

*Includes patients (N=741) from longer-term studies on TRAVATAN as monotherapy or as adjunctive therapy (C-97-71, C-97-72, C-97-79, C-97-73 and C-99-10).
**Includes patients 200 patients from C-97-71 on TRAVATAN monotherapy for up to 12 months.
***Includes 196 patients from C-97-71 on XALATAN monotherapy for up to 12 months.

A direct comparison was provided between TRAVATAN and XALATAN in clinical study C-97-71, which had a study duration of 12 months. The incidence of iris colour change was 2.3% for TRAVATAN, and 5.2% for XALATAN. The distribution over time appears to be comparable for both drugs with the occurrence having a threshold of approximately 3 months of initial therapy.

In the ongoing worldwide post marketing surveillance of TRAVATAN, 3 reports (reporting rate of 0.0002%) of iris hyper pigmentation have been received.

The CPMP in their Request for Supplementary Information asked the MAH to provide an update on whether the MAH has any iris histology from surgical specimens in TRAVATAN treated patients

developing increased iris pigmentation. The MAH responded that at present it has no such material, but this should be available from the planned study C-01-78 in patients undergoing trabeculectomy. This was acceptable to the CPMP.

Eyelash and periocular skin changes

Eyelash changes (colour, length, density, and/or thickness) have been reported in the literature for prostaglandin analogues and also occurred during the clinical trials with TRAVATAN. It is possible that termination of prostaglandin analogue treatment may reverse this effect but conclusive evidence has not yet been obtained. This is also true in respect of findings of peri-ocular skin changes. It has been reported in the literature that prostaglandin analogues may stimulate the melanogenesis in epidermal melanocytes and thereby probably mediate tanning of the skin. It is considered that these changes are also possibly reversible with discontinuing use of medication, but conclusive evidence is not yet available. The transit time of the basal layer to the stratified corneum is 4 to 5 weeks, and shedding of the cornified layer requires two more weeks. Thus it takes at least 7 weeks for skin pigmentation to disappear after discontinuing use of medication. In contrast, iris melanocytes remain stable and changes in iris pigmentation after prostaglandin use persist or regress very slowly.

Adverse events reported for eyelash changes were uncommon in the studies completed following the MAA with 1 patient (0.1%) with exposure to travoprost 0.0015% as monotherapy and 7 patients (0.8%) with exposure to travoprost 0.0040% as monotherapy experiencing events coding to hair disorder. Also, in the ongoing long-term safety study, 2 patients (2.8%) with exposure to travoprost 0.0015% as monotherapy (one case was related to the study medication an the remaining one was considered unrelated) and no patient with exposure to travoprost 0.0040% as monotherapy experienced events coding to trichiasis.

Macular oedema

Macular oedema, and particularly cystoid macular oedema (CME) has been reported in patients treated with prostaglandin analogues. However, a firm causal relationship has still not been proven using valid scientific methodology. There have been no reports to date in any clinical investigational study, completed or ongoing, of CME.

Eight cases had been reported in post-marketing surveillance reports (incidence inferior to 0.000303%). There is somewhat limited information available from these patients, but some evidence suggests that this is a class effect for prostaglandin analogues. However, the CPMP in the Request for Supplementary Information asked the MAH to analyse the observed cases of CME.

The MAH responded that since this variation application was submitted, there has been an additional report of CME filed via the post-marketing Spontaneous Adverse Event Reporting System, although this report does not meet the minimum reporting criteria. There are therefore a total of 9 reports of CME in the TRAVATAN post-marketing database. Due to the extremely small numbers of patients involved, any differentiation is difficult to justify. The data on patients who developed CME when treated with TRAVATAN does not allow a distinction between phakic/aphakic patients with or without torn posterior lens capsule.

The CPMP considered that the warning in section 4.4 should be reworded to state that caution is recommended when using TRAVATAN in aphakic patients, in pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular oedema.

Post marketing experience

A total of 2,532,140 units of TRAVATAN have been prescribed world wide between March 2001 and 30 September 2002. During this period the MAH received two hundred and seventy-one (271) spontaneous reports possibly associated with the use of TRAVATAN. One hundred and four of these reports fulfilled minimum reporting criteria.

TRAVATAN Eye Drops	N
Cases meeting minimum reporting criteria	104
Cases from health professionals with no identifiable patient	37
Cases from non-health professionals	130
TOTAL	271

During the period covered by this report, no serious attributable adverse events from clinical trials have been received or been published in the literature.
No serious case reports associated with the use of TRAVATAN, meeting minimum reporting criteria, have been received by the MAH's Department of Product Safety before the initial date of this safety report.

All spontaneous adverse events for TRAVATAN were extremely uncommon (≤0.00304%) based upon worldwide sales.

Including all spontaneous post-marketing reports, the most frequently reported ocular adverse events were ocular hyperaemia, ocular pain, ocular irritation, hair disorder (eyelash), and photophobia. Headache was the most frequently reported systemic adverse event. These events are similar in type to those reported in clinical trials with Travoprost 0.004% and are consistent with the current SPC for TRAVATAN.

Five cases (SOC Eye disorders: 2 cases, Cardiac disorders: 3 cases met the criteria for a serious report. All other adverse reactions received in the period covered by this report were non-serious.

Post-marketing ocular adverse events reported to date with TRAVATAN, but not observed in previous clinical studies included macular oedema (8 reports), IOP increase (6 reports), allergic reaction (4 reports), blindness (3 reports), and reaction aggravation (3 reports). Other ocular and non-ocular adverse events observed in post-marketing reports and not reported previously in clinical trials were isolated adverse events in small numbers of subjects (2 or less).

Eye disorders

The most frequently reported eye disorders were non serious and labelled (Ocular hyperaemia, Eye pain, Photophobia, Visual acuity reduced; Vision blurred; Eye irritation; and Growth eyelashes).
One case of iris hyper pigmentation has been reported.

Two serious cases were received in this period and classified under this SOC. In one case the report included retinal haemorrhage, blindness not otherwise specified, visual acuity reduced, ocular hyperaemia, and abnormal sensation in eye. In the other case blindness unilateral, eye pain, headache not otherwise specified were reported. Evaluation of these serious reports by the MAH indicated that underlying diseases in both cases are the most likely explanation for the loss of vision reported.

The CPMP, after review of first 6 month PSUR, requested specific monitoring of the following eye disorders:

Macular Oedema: as reported above.

Cycloplegia: Two cases were received during this reporting period. Neither case was considered serious. The information collected did not allow further analysis. Two other cases were coded as Accommodation disorder. In one case the event had resolved and patient resumed taking the product without further problems. In the other case, the accommodation disorder was not the primary event, but only one of eight non-serious complaints. No additional follow up was possible.

Specific literature searches had been implemented with no relevant results.

The MAH was asked in the Request for Supplementary Information to submit an updated review of all cases of intraocular inflammation and to discuss iritis and uveitis in more detail in particular any pre-disposing factors in the cases that might form a basis for a warning in section 4.4 of the SPC.

The MAH reviewed the adverse event codes of Flare, Cells, Iritis, and Uveitis from the twenty completed clinical studies in order to provide an update on intraocular inflammation seen in TRAVATAN monotherapy patients.

Overall, intraocular inflammation (determined by the codes of flare, cells, iritis and uveitis) occurs rarely. Overall, these events are non-serious, mild to moderate, usually resolve with or without treatment and generally do not interrupt patient continuation in the studies. No clear pattern of predisposing factors for iritis/uveitis with TRAVATAN is noted, except that 1 patient with uveitis had a history of this with other prostaglandin analogues. There were no other cases with a history of iritis/uveitis mentioned, and only a few patients had undergone prior ocular surgery.

The number of cases with TRAVATAN is presently small, but the CPMP proposed that a statement should be added to the TRAVATAN SPC to state that in patients with predisposing factors for iritis/uveitis, TRAVATAN can be used with caution."

Cardio-vascular events:

During the period covered by this PSUR, a total of ten reports were received that included events subsequently coded as cardiac disorders and three cases as vascular disorders.

Three cases were serious (2 cases of myocardial infarction, 1 case of hypertensive crisis and tachycardia). The MAH's assessment reveals other, more likely, causes for the reactions reported such as underlying pathologies or concomitant medications. The remaining seven cases were non serious and can be regarded as isolated events that could have more than one possible cause.

The three cases of vascular disorders received during this period were non serious and labelled (bradycardia, hypotension and hypertension).

None of the cases received reveals any safety concern related to specific effects of TRAVATAN upon the vascular system.

Clinical studies completed or ongoing since the product was first approved have not identified any cardiovascular events that would impact the safety profile.

No relevant new information related to cardiovascular effects of TRAVATAN has been found in the literature.

Nervous system disorders
All events in this SOC were classified as non-serious. The most frequently described reaction was Headache (n = 11), a labelled event, followed by Dizziness (n = 3), which was the primary reaction in only one case.

Respiratory thoracic and mediastinal disorders

All events were non-serious. The most frequently reported event was Asthma exacerbation (3 cases). In these patients, with pre-existing asthmatic disease, the current status and control of the illness was unknown, and direct causality is difficult to establish in such predisposed patients. However, there is an additional isolated case, where TRAVATAN allegedly caused Asthma Not Otherwise Specified.

In the Request for Supplementary Information the CPMP asked the MAH to discuss the studied exposure in patients with known asthma.

The MAH responded that including all studies with a TRAVATAN monotherapy arm, only 11 patients had a history of either previous or currently ongoing asthma. Of these 11 patients, only 1 had an adverse event for asthma. Additionally, six patients treated with TRAVATAN monotherapy had a history of either previous or currently ongoing COPD or emphysema. None of these patients had an adverse event related to COPD or emphysema exacerbation. Although only a small number of patients with known asthma, COPD or emphysema have been identified in clinical trials, based upon this data, no safety risks have been identified in this population of patients. The CPMP noted, however, that on review of the updated PSUR submitted a total of 3 spontaneous reports of asthma exacerbation were reported, plus 1 case of asthma and isolated cases of COAD exacerbation and dyspnoea. It is known that prostaglandin F2alfa has bronchoconstrictor effects and although a rare adverse event it can not be considered an unexpected adverse event.

Systemic allergic reactions

The MAH was also asked in the Request for Supplementary Information to give a fuller discussion on new reports from studies and marketing surveillance involving systemic allergic events.

Details of 2 new systemic adverse events from completed clinical studies since the MAA and seven post-marketing reports related to systemic allergic events were reviewed by the MAH. The 2 reports from clinical studies were of maculopapular rash and "skin disorder".

The CPMP considered that when looking at the fuller description of the spontaneous reports submitted, in the main they are not indicative of systemic allergy and that the extent of data is insufficient to require a change in the labelling.

Skin and subcutaneous tissue disorders
All events received are non-serious. The most commonly reported events were "Skin hyper pigmentation" and "Hair colour changes". These events are adequately explained as possible in the SPC.

Summary on safety

Globally, 3,622 patients encompassing all treatments studied are included in the submitted current analysis. Of these, 2,922 were described in the original MAA and 896 patients are providing new data.

Regarding the exposure across time, in the original MAA, there were no data on patient exposure beyond 12 months. In the application for first line therapy, there are safety and efficacy available data for 139 patients (study C-99-10) treated with travoprost for up to 48 months. Of these patients, 106 were treated for more than 3 years on either travoprost 15 μg/ml or travoprost 40 μg/ml.

The additional studies and new safety data confirm the established adverse events profile for TRAVATAN since the reported ocular and non-ocular adverse events in the additional 10 studies were similar in type, severity and intensity to those reported in the MAA and to those included in the current SPC for TRAVATAN. Therefore, no new safety concerns or risks have been identified based upon the adverse event data or other safety parameters for TRAVATAN in the additional short-term studies.

The most common ocular adverse events related to TRAVATAN monotherapy in the ongoing long-term study are similar to those reported in the initial MAA regarding type, severity and intensity. The ocular tolerability for TRAVATAN when it is administered beyond 12 months appears similar to the ocular tolerability in the short-term administration. Overall, post-marketing adverse events were generally similar in type to those observed in clinical studies with Travoprost 0.004%.

Two new studies have been performed and completed since the MAA and two ongoing studies are being carried out in order to further assess the iris pigmentation changes related to travoprost.

The submitted data appears to point out to the fact that changes on iris colouration are produced within the first two years of therapy, mainly, the first year, without no additional iris colour changes after the second year of therapy. Therefore, although the completion of the ongoing studies could provide definitive data on iris colour changes, the available data support the fist line indication for TRAVATAN based on the fact that no additional iris colour changes have been reported after the second year of therapy.

Regarding eyelash changes the most relevant study is still ongoing and definitive data will not be available until its finalisation. However, the complaints of eyelash changes seems to be very rare and it does not appear to be a clinically relevant issue that precludes the utilisation of TRAVATAN as first-line therapy.

Although a causal relationship between the use of prostaglandin analogues and the occurrence of CME has not been proven for travoprost, CME could be considered as a class effect for prostaglandin analogues.

5. Overall conclusions and benefit/risk assessment

Benefit/risk assessment

Quality

Pharmaceutical data show that the active substance and finished product are manufactured and controlled in a satisfactory way, resulting in a product of uniform quality suitable for ophthalmic use. A number of minor issues were unresolved at the time of the opinion and these will be dealt with as Follow up measures. These follow up measures have no impact on the benefit risk ratio and do not prevent a positive opinion.

Preclinical pharmacology and toxicology

Overall, the primary pharmacodynamic studies provided adequate evidence that travoprost is well tolerated and produces a significant reduction of IOP. The general pharmacology studies showed, that secondary pharmacological activity following systemic administration is generally unremarkable and the effects, as a result of the prostanoid receptor agonist activity of travoprost, occur at doses/concentrations many fold higher than those anticipated in clinical use.

The toxicity studies were, in general, uneventful. However, in view of the pronounced effects in the reproductive toxicity studies and the significant excretion into maternal milk, use of travoprost in pregnancy and lactation should be discouraged. This information has been included in the SPC.

Efficacy

Travoprost dosed once daily produced both clinically relevant and statistically significant IOP reductions when used as a monotherapy. The IOP reductions were maintained over the entire 6 to 12 month treatment periods. The CPMP concluded that Travoprost 0.0040% is numerically superior to travoprost 0.0015% in analyses on mean IOP efficacy and the rate of responders is superior with travoprost 0.0040%.

In comparison to timolol, travoprost has, in general, worse ocular tolerability and a limited knowledge on its mechanism of action and on the long-term adverse effects. Efficacy and safety may be comparable to that of latanoprost, indicated in patients that do not tolerate or have insufficient response to any other treatment. The applicant agreed with the recommendation of the CPMP and the wording of the indication in the SPC was been modified to only include the second line.

The efficacy of travoprost as adjunctive therapy to timolol has been studied in one pivotal trial. As no comparison to another active treatment (e.g. latanoprost) in adjunctive therapy was performed, there is information about the absolute efficacy of travoprost when added to timolol in patients not well controlled with timolol alone, but we do not know how it compares with other possible approved adjunctive therapies to timolol. When used adjunctively with timolol, travoprost produced both clinically relevant and statistically superior IOP reductions compared to vehicle. The IOP reductions were maintained over the entire 6-month treatment period. The differences between travoprost 0.004% and 0.0015% were not statistically significant. The CPMP raised a third major objection regarding the limitations of the indication in adjunctive therapy (limited data with brimonidine, absence of data with other antiglaucomatous agents). This has been solved and the wording of the SPC was modified in order to reflect these limitations.

The initial Marketing Authorisation application did contain comparative efficacy data to standard first line therapy (timolol) and another prostaglandin analogue (latanoprost) that showed similar efficacy of travoprost than with both comparators. In the application for first line therapy the long-term efficacy-safety study C-99-10 showed that the IOP reduction produced by TRAVATAN at the initiation of the study were consistently maintained throughout the study. Although the number of patients treated beyond 36 months was scarce (n=51), this can be taken as a further confirmation of the maintenance of the effect along the time. Taking into account the intended chronic use of this medicinal product this can be considered a clinically relevant characteristic. The findings are consistent with the data reported in the initial dossier. TRAVATAN has shown at least similar efficacy or superior efficacy to

standard therapy (timolol) with some characteristics that suggest its use as first line treatment (i.e. different contraindications, more commodity of use because of a single administration per day).

Safety

The safety profile of travoprost is in accordance with that expected from the pre-clinical studies. Most of adverse events were mild and non-serious and 6.2% of the of the patients treated with travoprost 0.0040% discontinued treatment due to any adverse event, related or unrelated to the therapy. Most related adverse reactions were ocular, mainly hyperemia, burning or stinging, pruritus, iris discolouration and others. With regard to related systemic adverse reactions, they appeared in about 4% of patients and the most frequently reported reaction was headache. No deaths or other serious events related to Travoprost 15 or 40 μg/ml were reported during the studies. No changes in biochemical or haematological parameters have been found.

Ocular side effects were comparable to those described with latanoprost and in the view of the CPMP the tolerability of travoprost is not inferior to latanoprost. In comparison to timolol, the frequency of ocular side effects is higher with travoprost than with timolol. On the other hand, less systemic cardiovascular and respiratory effects could be expected although this has not been evidenced in the submitted clinical trials.

In the application for first line therapy data were submitted on 896 additional patients including safety data for 139 patients (study C-99-10) treated with travoprost for up to 48 months. The additional safety data confirm the established adverse events profile for TRAVATAN. The reported ocular and non-ocular adverse events were similar in type, severity and intensity to those reported in the MAA and to those included in the current SPC for TRAVATAN.

Ocular tolerance of TRAVATAN is accepted to be somewhat poorer than timolol, with high rates of ocular hyperaemia in particular, although events are usually not severe and this is balanced by a more favourable systemic safety profile.

The majority of increased iris pigmentation cases occurred within 1 year of starting therapy and most often within 2 years of treatment. It appears to reach a maximal observable level with continued treatment up to 4 years. Limited data seem to suggest that increased iris pigmentation is not associated with any other symptoms. Data indicate that if treatment is stopped (and in 10 cases where prostaglandin analogues were continued), iris changes do not reverse but neither do they continue to progress during 2 years of follow-up. The mechanism of action for increased iris pigmentation is not fully understood, but is thought to result from increased melanogenesis rather than from increased cell division.

Benefit/risk assessment

Travoprost is a synthetic prostaglandin $PGF_{2\forall}$ analogue proposed to be used in topical ocular administration in open angle glaucoma. The mechanisms involved in the decrease of the intraocular pressure (IOP) are not well known but are supposed to be related to the increase of the aqueous humour outflow through the uveoscleral pathway. Some uncertainty exists about the effects on other tissues in the eye and the possible long-term effects of such an inflammatory mediator.

Two different concentrations (0.0015% and 0.0040%) were studied in pivotal clinical trials without differences in efficacy and marginal differences in safety. Although the applicant initially proposed both dosages to be approved, the CPMP concluded that Travoprost 0.0040% is numerically superior to travoprost 0.0015% in analyses of mean IOP efficacy and the rate of responders is superior with travoprost 0.0040%. There thus is no justification for the co-existence of both concentrations.

Travoprost lowers IOP in monotherapy with a slightly higher efficacy than timolol at the cost of a worse ocular tolerability. When compared to a similar product, latanoprost, efficacy and safety seem comparable. Timolol is the first line product to decrease IOP in open angle glaucoma and although efficacious and well tolerated has some limitations in certain populations due to the potential systemic

side effects (mainly bronchoconstriction). Therefore, travoprost could be useful for some patients where timolol (or other alternative products such carbonic anhydrase inhibitors, α2 agonists) can not be used. Due to the fact that in clinical trials it shows a higher decrease of IOP and a higher rate of responders, it could be accepted also to treat patients with insufficient response to timolol, although a specific trial in these patients is lacking.
The combined therapy of travoprost plus timolol obtains an additional decrease of IOP in patients with insufficient control with timolol alone. However, some ocular adverse reactions also increase and, unfortunately, there are not comparative data to other accepted similar combined therapies (i.e. timolol plus latanoprost). In addition, only one trial where travoprost is added to timolol has been performed and there is no information from controlled clinicaltrials of the combination of trvoprost with other products also indicated when timolol cannot be used (carbonic anhydrase inhibitors, a2 agonists). Therefore, although the adjunctive therapy is an interesting place in therapeutics of the product, it can only be accepted taking into account these limitations and with a consequent wording in the SPC.

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered initially that the benefit/risk profile of Travatan was favourable in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma who are intolerant or insufficiently responsive to another intraocular pressure lowering medication, as monotherapy or as adjunctive therapy. However, following the assessment of new data submitted in the context of a Type II variation the CPMP considered that a current better understanding of the mechanism of action of prostaglandin analogues, as well as reassuring long term safety data available for travoprost supported the use of TRAVATAN as a first-line antiglaucoma therapy. Furthermore, although beta-blockers are still the well-established initial therapy it should be recognised that prostaglandin analogues may be a convenient alternative in some patients due to the initial good efficacy, which is sustained over time, the less frequent administration, a more favourable systemic safety and contraindications profile. The CPMP therefore considered that the benefit/risk profile of Travatan is favourable in the treatement of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.