

Latanoprost

An Update of its Use in Glaucoma and Ocular Hypertension

Caroline M. Perry, Jane K. McGavin, Christine R. Culy and Tim Ibbotson

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

A. Alm, Department of Ophthalmology, University Hospital of Uppsala, Uppsala, Sweden; H. DuBiner, Clayton Eye Center, Morrow, Georgia, USA; F.T. Fraunfelder, School of Medicine, Oregon Health Sciences University, Portland, Oregon, USA; P.H. Hoyng, Department of Experimental Ophthalmology, Netherlands Ophthalmology Research Institute, Amsterdam, Netherlands; Y. Kitazawa, Akasaka Kitazawa Eye Clinic, Tokyo, Japan; S. Law, Jules Stein Eye Institute, University of California, Los Angeles, California, USA; A. Martinez, Galician University Institute of Ophthalmology, Santiago, Spain; H.K. Mishima, Department of Ophthalmology, Hiroshima University, Hiroshima, Japan; R. Susanna, University of Sao Paulo, Department of Ophthalmology, Sao Paulo, Brazil.

Data Selection

Sources: Medical literature published in any language since November 1996 on latanoprost, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'latanoprost' or 'PHXA41'. EMBASE search terms were 'latanoprost'. AdisBase search terms were 'latanoprost' or 'PHXA41'. Searches were last updated 1 May 2003.

Selection: Studies in patients with glaucoma or ocular hypertension who received latanoprost. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: latanoprost, glaucoma, ocular hypertension, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

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Summary

Abstract

Latanoprost (Xalatan®) is an ester analogue of prostaglandin F_{2α} that reduces intraocular pressure (IOP) by increasing uveoscleral outflow. The IOP-lowering efficacy of latanoprost 0.005% lasts for up to 24 hours after a single topical dose, which allows for a once-daily dosage regimen.

In patients with ocular hypertension or open-angle glaucoma, a single drop of latanoprost 0.005% solution (about 1.5µg) administered topically once daily reduced diurnal IOP by 22 to 39% over 1 to 12 months' treatment in well-controlled trials; efficacy was maintained during treatment periods of up to 2 years. At this dosage, latanoprost was significantly more effective than timolol 0.5% twice daily in 3 of 4 large, double-blind, randomised studies, was generally as effective as bimatoprost or travoprost, and was significantly more effective than dorzolamide, brimonidine or unoprostone. Furthermore, in patients whose IOP was poorly controlled with timolol, switching to latanoprost monotherapy was at least as effective at lowering IOP as adding dorzolamide or pilocarpine to the regimen. Latanoprost has also shown significant additive effects when used in combination with one or more other glaucoma medications. The fixed combination of latanoprost plus timolol was significantly more effective than either of its individual components in two double-blind randomised studies and more effective than the fixed combination of dorzolamide and timolol in a 3-month, evaluator-masked study.

Data in patients with angle-closure glaucoma are limited, but in patients with elevated IOP after undergoing iridotomy, latanoprost 0.005% once daily was significantly more effective than timolol 0.5% twice daily at reducing IOP over 12 weeks of treatment in a large double-blind, randomised study.

Latanoprost is generally well tolerated and, unlike timolol, induces minimal systemic adverse events. In well-controlled, 6-month trials, the most commonly occurring drug-related ocular events in latanoprost recipients were mild to moderate conjunctival hyperaemia (3 to 15%) and iris colour change (2 to 9%); these seldom required patient withdrawal although the latter may be permanent.

Latanoprost 0.005% as a single daily drop has shown good IOP-lowering efficacy in patients with open-angle glaucoma or ocular hypertension and does not

produce the cardiopulmonary adverse effects associated with β -blockers. Thus, latanoprost is a valuable addition to the first-line treatment options for patients with open-angle glaucoma or ocular hypertension. In addition, adjunctive treatment with latanoprost in patients who are refractory to β -blocker therapy is a viable, second-line treatment option. Although preliminary findings are promising, wider clinical experience is required to define the place of latanoprost in the treatment of angle-closure glaucoma.

Pharmacodynamic Properties

Latanoprost is an ester prodrug analogue of prostaglandin $F_{2\alpha}$ with a high selectivity for the FP subtype of prostanoid receptors. Like other topically applied prostaglandins, latanoprost reduces intraocular pressure (IOP) by increasing uveoscleral outflow facility.

IOP reductions were maximal within 8 to 12 hours after a single topical dose of latanoprost (0.005%), and IOP remained below pretreatment levels for at least 24 hours. In addition, latanoprost showed little or no effect on aqueous humour flow, tonographic or fluorophotometric outflow facility, and did not disrupt the blood-aqueous barrier over short-term or long-term treatment. It is thought that the iridial darkening induced by latanoprost is due to enhanced melanin production.

Latanoprost 0.005% once daily either increased or had no appreciable effect on ocular circulation in patients with ocular hypertension or open-angle glaucoma. In one investigation, latanoprost increased diurnal ocular perfusion pressure to a significantly greater extent than timolol in patients with normal-tension glaucoma.

Results from one study investigating the effects of latanoprost in *in vitro* and/or *in vivo* models of retinal injury suggest that this agent may have neuroprotective effects.

Pharmacokinetic Properties

In patients undergoing cataract surgery the mean maximum concentration ($C_{\max}$) of latanoprost in the aqueous humour was 32.6 $\mu\text{g/L}$, the elimination half life ($t_{1/2}$) was 2.5 hours and the concentration 24 hours after administration was $\leq 0.2 \mu\text{g/L}$.

Following topical administration of latanoprost (30 μL of a 50 $\mu\text{g/mL}$ solution), $t_{1/2}$ was 17 minutes, the area under the latanoprost plasma concentration time curve was 34 $\text{ng}\cdot\text{h/L}$, and volume of distribution was 0.36 L/kg. Plasma $C_{\max}$ after topical application of latanoprost was 53 ng/L after 5 minutes.

In healthy volunteers, 87.9% of a radiolabelled latanoprost dose was recovered in the urine and 15.3% in the faeces after topical administration.

Clinical Efficacy

The IOP-lowering efficacy of latanoprost ophthalmic solution (0.005%; 50 $\mu\text{g/mL}$) has been evaluated in patients with ocular hypertension or open-angle glaucoma, angle-closure glaucoma and other types of glaucoma. Latanoprost was administered as a single drop (about 1.5 μg) once daily in all studies (unless otherwise indicated).

Open-Angle Glaucoma or Ocular Hypertension: In well-controlled clinical trials including patients with open-angle glaucoma or ocular hypertension (IOP $\geq 21\text{mm Hg}$), monotherapy with latanoprost reduced IOP levels by 22 to 39% over 1 to 12 months' treatment. Latanoprost was significantly more effective than timolol 0.5% twice daily in 3 of 4 large ($n = 163$ to 267) randomised, double-blind trials. In these studies, mean baseline diurnal IOP was reduced by 6.2 to 8.6mm Hg (27 to 35%) with latanoprost and 4.4 to 8.3mm Hg (19 to 33%) with timolol over 3 or 6 months of treatment. Latanoprost demonstrated a stable long-term

IOP-lowering effect in 1- or 2-year continuations of these trials, with no sign of diminishing effect during prolonged treatment.

In other randomised studies, latanoprost was generally as effective as bimatoprost (0.3% once daily) or travoprost (0.0015 or 0.004% once daily), and was significantly more effective than dorzolamide (2% three times daily), brimonidine (0.2% twice daily), or unoprostone (0.12 or 0.15% twice daily) at reducing IOP over 1 to 12 months' treatment.

In patients who had elevated IOP despite timolol treatment, switching to latanoprost monotherapy was at least as effective at reducing diurnal IOP as adding dorzolamide (2% twice daily) or pilocarpine (2% three times daily) to the regimen: mean diurnal IOP was reduced by 19 to 26%, 17 to 21% and 19 to 20%, respectively, over 6 weeks' to 6 months' treatment in randomised studies (n = 35 to 197).

The fixed combination of latanoprost plus timolol was significantly more effective than either of its individual components in two 6-month double-blind randomised studies and was also more effective than the fixed combination of dorzolamide plus timolol in a 3-month, evaluator masked study. When added to existing therapy with a β -blocker (usually timolol), latanoprost was significantly more effective than pilocarpine (2% three times daily) and dorzolamide (2% twice daily), and as effective as brimonidine (0.2% twice daily) at reducing IOP in randomised studies. Mean IOP was reduced by 24 to 32% with adjunctive latanoprost, 19 to 21% with adjunctive pilocarpine, 20% with adjunctive dorzolamide and 22% with adjunctive brimonidine. Latanoprost also demonstrated additive effects when used in combination with a variety of other IOP-lowering medications including dipivefrine, acetazolamide, dorzolamide and pilocarpine (but not unoprostone) in other studies.

In patients who had persistently elevated IOP despite receiving two or more IOP-lowering medications, latanoprost reduced IOP by a further 16 to 18% in noncomparative trials. In the only randomised study, latanoprost showed similar IOP-lowering efficacy to brimonidine 0.2% twice daily when these drugs were added to therapy with a β -blocker combined with pilocarpine or dorzolamide.

Angle-Closure Glaucoma: In patients who had elevated IOP despite iridotomy and/or iridectomy (including patients of Asian descent), latanoprost (0.005% once daily) was significantly more effective than timolol (0.5% twice daily) in two double-blind, monotherapy trials (8.2 and 8.8mm Hg vs 5.2 and 5.7mm Hg for latanoprost vs timolol at 12 and 2 weeks, respectively).

As adjunctive therapy in a small nonblind trial (patients had undergone iridectomy and were receiving combined treatment with β -blockers and pilocarpine with or without oral carbonic anhydrase inhibitors), latanoprost rapidly decreased mean IOP.

Other Types of Glaucoma: In randomised studies in patients with normal-tension glaucoma or steroid-induced glaucoma, latanoprost (0.005% once daily) displayed similar IOP-lowering efficacy to timolol 0.5% twice daily over 3 weeks or 4 months' treatment, respectively. In patients with pigmentary glaucoma (n = 36), latanoprost produced significantly greater reductions in IOP than timolol after 12 months therapy (5.9 vs 4.6%).

Tolerability

Overall, ocular-related adverse effects observed in patients with glaucoma who received latanoprost were mild to moderate in severity and the majority resolved after discontinuation of treatment. Treatment with latanoprost may cause mild conjunctival hyperaemia, iridial darkening and eyelash changes. Increased iridial pigmentation did not resolve upon cessation of latanoprost in patients followed for 2 years.

An increase in the severity and recurrence of herpes simplex virus keratitis has been reported after initiation of latanoprost therapy and caution is advised in patients with a history of herpes. Anecdotal evidence has suggested development of cystoid macular oedema as a potentially serious adverse effect associated with latanoprost treatment in patients with independent risk factors. Anterior uveitis has also been observed in approximately 1% of patients receiving latanoprost and is resolved with corticosteroid therapy. Administration of latanoprost to patients with active uveitis at the time of treatment may or may not aggravate the condition, but does not appear to lower IOP.

Latanoprost-related systemic adverse events are infrequent (unlike those induced by timolol) but include respiratory complications and headache. A similar incidence of adverse effects has been observed in short-term (range 30 days to 8 weeks) randomised studies of latanoprost with the prostaglandins bimatoprost or unoprostone, although in one study unoprostone recipients experienced more frequent adverse events than latanoprost recipients. Significantly more conjunctive hyperaemia and increased eyelash growth was reported in patients who received bimatoprost than latanoprost for 3 months and headache was more frequently seen in latanoprost than bimatoprost patients. Latanoprost has also shown a similar incidence of adverse effects to both dorzolamide and brimonidine; systemic effects are more pronounced with dorzolamide.

Dosage and Administration

In the US, Europe and Japan latanoprost is approved for first-line use in patients with open-angle glaucoma or ocular hypertension.

A single drop of latanoprost 0.005% ophthalmic solution (about 1.5µg) once daily is the recommended dosage.

The drug should be used cautiously in patients with renal or hepatic impairment and in patients with active intraocular inflammation (e.g. iritis, uveitis). Contact lenses should be removed before administration of latanoprost.

1. Introduction

Glaucoma is the second leading cause of irreversible vision loss in the world, accounting for approximately 15% of blindness worldwide.^[1] It is estimated that of the 67 million people worldwide affected by this disorder, 6.7 million are bilaterally blind as a result.^[2] Although glaucoma can occur at any age, the disorder is most common in elderly patients.^[3,4] Population studies show a dramatic rise in glaucoma prevalence after the age of 40 years. Indeed, in the US,^[5,6] the prevalence of glaucoma in individuals

aged ≥70 years is approximately 4- to 10-fold higher than in persons in their forties.^[3]

The term 'glaucoma' refers to a group of eye disorders characterised by progressive optic neuropathy and distinctive changes in the optic nerve head and the visual field.^[3,4] Several variants of glaucoma exist, but the main types are open-angle glaucoma (the most prevalent form in Caucasian and African populations) and angle-closure glaucoma (the most prevalent form in Asian and Eskimo populations). These can be further divided into subtypes accord-

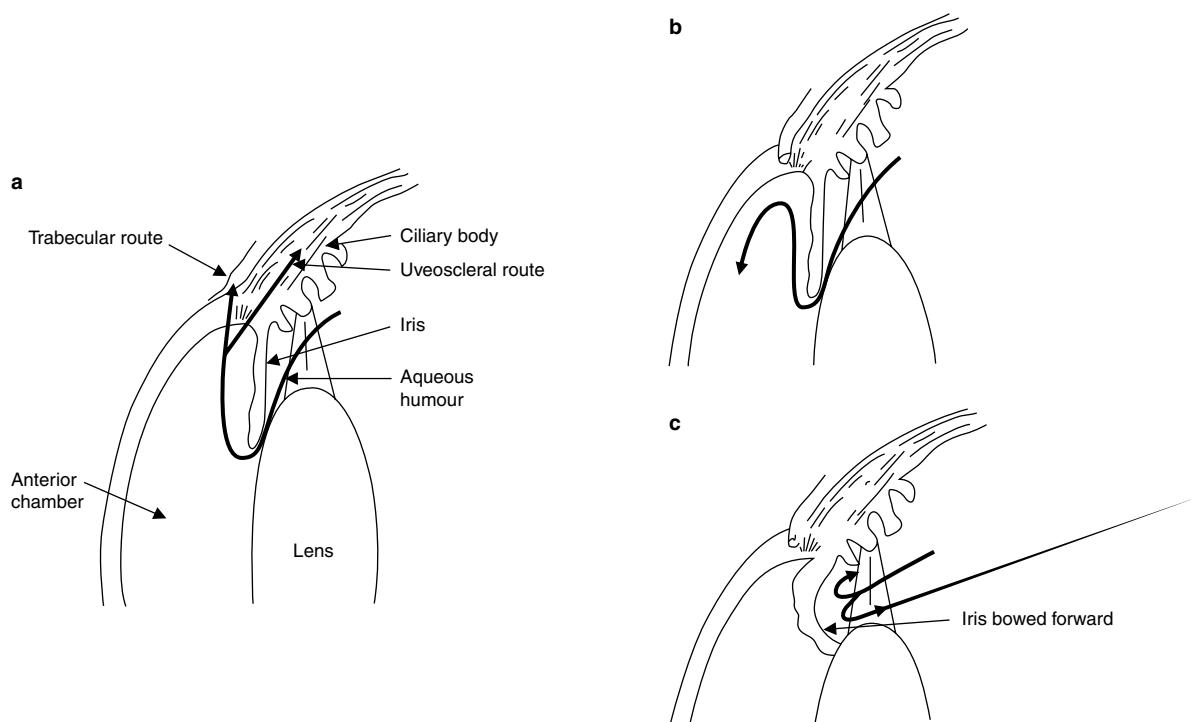


Fig. 1. Anatomical features and flow of aqueous humour in the human eye under normal conditions (a), in primary open-angle glaucoma (b) and in angle-closure glaucoma (c).^[12,13]

ing to aetiology (i.e. congenital, primary or secondary).^[3,4]

Glaucomatous damage is usually preceded or accompanied by an elevated intraocular pressure (IOP) which is caused by an imbalance between aqueous humour production and outflow in the eye. In the normal eye, aqueous fluid is produced by the ciliary body and flows through the posterior chamber and into the anterior chamber, then out through the trabecular network into the venous system; some fluid is also drained via the uveoscleral pathway through the iris root and ciliary body (figure 1a).^[7]

In open-angle glaucoma, the trabecular meshwork is open and unobstructed by the iris (figure 1b), but aqueous drainage is impaired. Optic neuropathy usually occurs gradually and visual impairment can take years to develop. Elevated IOP (usually defined as an IOP >21mm Hg) is considered a major risk factor for glaucoma and visual loss in patients with open-angle glaucoma;^[8] however,

some patients show optic nerve damage with relatively low IOP (normal-tension glaucoma), while others with persistent and pronounced IOP elevation (ocular hypertension) may never show such damage.^[3] These observations suggest that additional factors, such as vascular abnormalities,^[9] may play an important role in glaucomatous damage.^[3] Patients with open-angle glaucoma are usually managed with topical or oral hypotensive medications before surgical intervention is considered.^[3,10] Treatment to reduce IOP is also recommended in patients with normal-tension glaucoma and those with ocular hypertension who have other risk factors for glaucoma.^[3,10]

In patients with angle-closure glaucoma, the trabecular meshwork in the angle of the eye becomes obstructed by the iris and aqueous outflow is blocked (figure 1c). An acute attack of angle-closure glaucoma can cause a rapid and precipitous rise in IOP that can lead to blindness within hours or days if

not quickly treated. Management of these patients usually involves laser or surgical intervention (e.g. laser peripheral iridotomy) to create an opening for aqueous outflow through the iris, or along the iris through the pupil, but patients often require additional therapy with topical or oral ocular hypotensive medications if IOP remains elevated.^[4]

Secondary glaucomas can be caused by substances mechanically blocking the anterior chamber angle (e.g. pigmentary and pseudoexfoliation glaucoma) or can result from alterations in the structure and function of the trabecular meshwork due to insults such as trauma, inflammation or ischaemia.^[3] The goals and approaches to treatment for these patients are similar to those for open-angle glaucoma.^[3]

Latanoprost (PHAX41, Xalatan®¹) is the first agent in a relatively new class of topical glaucoma drugs, the so-called prostaglandin analogues, to become commercially available. The pharmacology and clinical efficacy of latanoprost in patients with open-angle glaucoma and ocular hypertension were extensively reviewed in *Drugs & Aging* in 1996;^[11] this article provides an update on its use in these patients, and also reviews new clinical data investigating the potential role of latanoprost in other types of glaucoma, in particular, angle-closure glaucoma.

2. Pharmacodynamic Properties

Latanoprost is an ester prodrug analogue of prostaglandin F_{2α} with a high selectivity for the FP subtype of prostanoid receptors. The pharmacodynamic properties of latanoprost have previously been reviewed;^[11] this section provides an update on its pharmacodynamic profile.

2.1 Mechanism of Action

Like other topically applied prostaglandins, latanoprost is believed to reduce IOP by increasing uveoscleral outflow.^[14,15] This is in contrast to other classes of antiglaucoma medications which act by increasing aqueous humour outflow via the trabecular meshwork or by inhibiting aqueous humour pro-

duction. Although the exact mechanisms are still not entirely clear, it appears that prostaglandins open the uveoscleral pathway in the ciliary muscle by reducing the extracellular matrix in the spaces among ciliary muscle fibres.^[14,15] Relaxation of the ciliary muscle may also contribute to the increased outflow.^[14,16,17]

The ciliary muscle contains several different prostaglandin receptors, mainly FP and EP2 receptors.^[18,19] Activation of these receptors stimulates several intracellular second messenger mechanisms^[20,21] which are thought to activate the biosynthesis of matrix metalloproteinases (MMPs), a family of neutral proteinases that have a lytic effect on extracellular matrix molecules.^[22] This is supported by experiments in cultured human ciliary muscle cells and monkey eyes which showed an upregulation of MMPs 1, 2, 3 and 9,^[23-27] followed by a decrease in collagen types I, III and IV after treatment with latanoprost, PGF_{2α} or PGF_{2α}-IE.^[25,28,29]

2.2 Ocular Effects

In healthy volunteers or patients with ocular hypertension or open-angle glaucoma, IOP reductions were maximal within 8 to 12 hours after a single topical dose of latanoprost (0.005 or 0.006%), and IOP remained below pretreatment levels for at least 24 hours.^[30-34] During 24-hour IOP measurements, latanoprost showed similar efficacy during daytime and night-time hours and circadian fluctuations were minimal (see section 4).^[31-35] IOP reductions were greatest when latanoprost was administered once rather than twice daily;^[36-38] the reason for this is not entirely clear but may be related to a loss of some of the effect due to development of receptor subsensitivity.^[39] Following discontinuation of latanoprost after treatment for 6 to 12 months, IOP is restored to pretreatment levels after a few (>2) weeks.^[40]

As mentioned in section 2.1, IOP reductions are believed to be due to increased uveoscleral outflow. An increase in uveoscleral outflow has been shown directly in monkeys,^[14] and indirectly in healthy

¹ Use of tradename is for product identification purposes only and does not imply endorsement.

volunteers receiving latanoprost 0.005 or 0.006% once or twice daily.^[14,31,41,42] Latanoprost had no effect on aqueous humour flow,^[41-43] and showed little^[41] or no^[42] effect on tonographic or fluorophotometric outflow facility in human volunteers or patients. Furthermore, no signs of blood-aqueous barrier (BAB) breakdown have been demonstrated during short-term^[30,41,43,44] or long-term (12 months)^[40] latanoprost treatment in volunteers or patients with ocular hypertension or open-angle glaucoma. However, BAB was disrupted following latanoprost treatment in one study in patients with early postoperative pseudophakic eyes,^[45] which may account for the apparently increased risk of cystoid macular oedema observed in these patients during latanoprost treatment (see section 5.1.4).

Studies evaluating the effects of latanoprost (0.005% once daily) on ciliary body thickness show variable results. Latanoprost reduced,^[46] increased^[47] or had no effect^[48] on ciliary body thickness as measured by ultrabiomicroscopy (UBM) in healthy, hypertensive or glaucomatous human eyes. In another UBM study in healthy volunteers, latanoprost reduced accommodative capacity, which was assumed by the investigators to be the functional consequence of a reduction of ciliary body thickness.^[49]

A short-term study (n = 37) showed that there were no significant effects of latanoprost or timolol on the ocular surface and tear secretion after 1 month of treatment in patients with open-angle glaucoma or ocular hypertension.^[50] Latanoprost and timolol had equivalent and minimal effects on corneal endothelial cell density and thickness after 1 year of therapy in patients with open-angle glaucoma and ocular hypertension with normal corneas in another trial (n = 369).^[51]

One of the most common adverse effects observed with latanoprost is iridial darkening (see section 5.1.2). Various *in vitro* and *in vivo* studies indicate that this is due to enhanced melanin production associated with a prostaglandin-induced increase in tyrosinase activity (the rate-limiting step in melanogenesis).^[52-56] Prostaglandins A₂ and E₁ stimulated growth and melanogenesis in cultured iridial

melanocytes *in vitro*,^[57] however, latanoprost and other prostaglandins had no effect on melanocyte proliferation.^[53-55,58]

2.3 Vascular Effects

The effects of latanoprost (0.005% once daily) on ocular circulation in normal or glaucomatous human eyes have been investigated using a range of different methods with variable results. In general, latanoprost increased or had no appreciable effect on ocular blood flow.

Nicolela et al.^[59] demonstrated no change in blood velocity or vascular resistivity of the retrobulbar vessels over 3 weeks of latanoprost or timolol (0.5% twice daily) treatment in patients with open-angle glaucoma or ocular hypertension. Similarly, blood flow was unaffected by latanoprost (0.005% once daily) in another trial, but was significantly increased with brimonidine (0.2% twice daily) after 1 month of treatment.^[60]

In other randomised studies, latanoprost significantly increased pulsatile ocular blood flow in healthy volunteers^[61,62] and in patients with open-angle glaucoma^[63] or normal-tension glaucoma;^[64] in contrast, pulsatile ocular blood flow remained unchanged^[61] or was reduced^[63] in eyes treated with timolol in two of these investigations. In a double-blind, randomised, crossover trial in patients with normal tension glaucoma,^[65] latanoprost increased diurnal ocular perfusion pressure to a greater extent than timolol (by 8 vs 2%; p < 0.05).

The effect of latanoprost on the optic nerve circulation has been investigated in two trials in healthy volunteers. In one investigation, a single application of latanoprost had no effect on optic nerve head or peripapillary retinal blood flow (measured using Heidelberg regional flowmetry);^[66] however, optic nerve blood flow was significantly increased after latanoprost was administered daily for 1 week in another trial (measured by the laser speckle method).^[67] The significance of ocular blood flow in the management of glaucoma remains to be determined.

2.4 Neuroprotective Effects

Results of one study investigating the effects of latanoprost in *in vitro* and/or *in vivo* models of retinal injury suggest that this agent may have neuroprotective effects;^[68] however, more confirmatory data are required. In this study,^[68] latanoprost and its acid metabolite reduced glutamate- and hypoxia-induced cellular injury in cultured human retinal cells (as measured by a reduction in lactate dehydrogenase release). This protective effect was observed at concentrations of 0.1 to 0.001 $\mu\text{mol/L}$ for latanoprost and 1 to 0.01 $\mu\text{mol/L}$ for its active acid metabolite (section 3). Latanoprost treatment (0.01 mg/kg/day for 3 days) also reduced lactate accumulation in retinal tissues of rats subjected to acute ischaemia or a transient increase in IOP, suggesting that this agent has protective effects *in vivo* as well.^[68]

3. Pharmacokinetic Properties

The pharmacokinetics of latanoprost have been reviewed previously in *Drugs & Aging*.^[11] Pharmacokinetic investigations of latanoprost in humans are limited to one study in which latanoprost was administered as tritium-labelled latanoprost.^[69,70]

In 18 patients undergoing cataract surgery, the mean maximum concentration (C_{max}) of latanoprost in the aqueous humour was 32.6 $\mu\text{g/L}$ (detected $\approx$ 2.5 hours following a single 30 μL drop of latanoprost 50 $\mu\text{g/mL}$).^[69] The elimination half-life ($t_{1/2}$) of latanoprost from the aqueous humour was 2.5 hours and the concentration 24 hours after administration was ≤ 0.2 $\mu\text{g/L}$.^[69]

Following topical administration of latanoprost (30 μL of a 50 $\mu\text{g/mL}$ solution) to four healthy volunteers, $t_{1/2}$ was 17 minutes, the area under the latanoprost plasma concentration time curve was 34 $\text{ng}\cdot\text{h/L}$, and the volume of distribution was 0.36 L/kg.^[69] The C_{max} in the plasma following topical application of latanoprost was 53 ng/L after 5 minutes.^[69]

Latanoprost undergoes extensive first-pass metabolism in the liver via β -oxidation to its (1, 2)-dinor and (1, 2, 3, 4)-tetranor metabolites which are predominantly eliminated via the kidneys.^[71] In healthy

volunteers, 87.9 and 15.3% of a radiolabelled latanoprost dose was recovered in the urine and faeces after topical administration.^[69,70]

4. Clinical Efficacy

The clinical efficacy of latanoprost ophthalmic solution (0.005%; 50 $\mu\text{g/mL}$) in patients with open-angle glaucoma or ocular hypertension has been reviewed previously by Patel and Spencer;^[11] this section provides an update on this indication (section 4.1), and will also review data in angle-closure glaucoma (section 4.2) and other types of glaucoma (section 4.3). In these indications, latanoprost has been studied as both monotherapy and as adjunctive treatment.

As outlined in the previous review,^[11] a single drop of latanoprost 0.005% solution (about 1.5 μg) once daily has been established as the most effective dosage regimen.^[11,72,73] Unless otherwise stated, this is the dosage used in reported studies.

The peak IOP-lowering effect of latanoprost occurs between 8 and 12 hours after instillation (section 2.2);^[71] therefore, IOP measurements taken in the morning represent the peak effect of latanoprost for patients administering the drug in the evening. All agents discussed in this section were administered topically unless otherwise stated.

4.1 Open-Angle Glaucoma or Ocular Hypertension

The patient population in these studies comprised a mix of those with ocular hypertension or open-angle glaucoma; patients with capsular, pigmentary and pseudoexfoliation glaucoma were also included. A baseline IOP ≥ 22 mm Hg with or without medication was generally required for study entry.

The minimum patient age was 18 years in most trials and the mean age ranged from 56 to 70 years; however, some trials restricted enrolment to patients aged ≥ 40 ^[74-79] or ≥ 60 ^[37] years.

Typical exclusion criteria included angle-closure glaucoma, eye surgery or laser treatment within the preceding 6 months, contact lens use, severe dry eye syndrome, ocular inflammation in the past 3 months, concomitant medication known to affect IOP, pre-

vious ocular trauma or any condition that prevented reliable applanation tonometry.

The primary endpoint in most trials was the mean reduction in IOP from baseline. Measurement of IOP varied from study to study: most studies assessed changes in diurnal IOP which were calculated as the mean of three daily measurements taken between 8am to 6pm; however, some studies investigated IOP over a 12-^[80,81] or 24-hour period,^[35,82,83] and/or measured IOP at specific time points (usually in the morning at the peak drug effect of latanoprost).^[81,84,85] Double-blind comparisons with other glaucoma medications given at least twice daily were also double-dummy in design.

4.1.1 Monotherapy

Latanoprost has been compared with a number of other topical ocular hypotensive agents including the β -blocker timolol (as monotherapy and as one component of combination therapy), the carbonic anhydrase inhibitor dorzolamide, brimonidine (an α_2 -receptor stimulant), and the prostaglandin analogues bimatoprost, travoprost and unoprostone in randomised clinical trials (table I). Many trials were double-blind, including all comparisons with timolol, while others were single-blind or nonblind (table I). All^[74-77,80,81,85-95] but one^[96] are fully published. Treatment duration was 1 to 12 months. Patients in these studies were either previously untreated or had withdrawn from other pressure-lowering therapy (with no more than two other agents) prior to the trial; however, specific details on previous treatment history were generally not provided (with the exception of a few trials^[77,82,83,87,89,93]). Only one study^[89] discussed results in previously-treated versus treatment-naïve patients separately.

In well-controlled clinical trials including patients with open-angle glaucoma or ocular hypertension (IOP ≥ 21 mm Hg), monotherapy with latanoprost reduced IOP levels by 22 to 39% over 1 to 12 months' treatment (table I).

Compared with Timolol

Latanoprost was significantly more effective than timolol 0.5% twice daily in 3 of 4 large ($n = 163$ to 267) double-blind randomised trials conducted in Scandinavia,^[74] the US,^[76] and Japan,^[87] and was of

equivalent efficacy in the UK trial.^[75] In these studies, mean baseline diurnal IOP was significantly ($p < 0.05$) reduced by 6.2 to 8.6mm Hg (27 to 35%) with latanoprost and 4.4 to 8.3mm Hg (19 to 33%) with timolol over 3^[87] or 6^[74-76] months of treatment.

In 1- or 2-year extensions of these trials,^[97-100] latanoprost demonstrated a sustained long-term IOP-lowering effect, with no sign of a diminishing effect during prolonged treatment.

Overall, latanoprost also appears to have a more consistent 24-hour IOP-lowering effect than timolol, particularly during the evening hours as shown in small ($n = 20$ to 77), randomised crossover studies including the gel forming solution.^[35,82,83]

Mean reductions in IOP were lower with latanoprost than with timolol 0.5% during both the daytime and night-time hours ($p \leq 0.05$)^[82,83] and at study end ($p < 0.001$)^[83] in separate 1-month trials. Latanoprost produced a more uniform IOP-lowering effect than timolol in the latter trial; there were no significant differences between daytime and night-time decreases with latanoprost, unlike timolol which reduced IOP to a larger extent during the day ($p = 0.04$).^[83] Latanoprost and timolol 0.5% had similar efficacy in a 2-month trial.^[35]

Compared with Other Treatments

Latanoprost was generally as effective as bimatoprost (0.3% once daily) or travoprost (0.0015 or 0.004% once daily), and was significantly more effective than dorzolamide (2% three times daily), brimonidine (0.2% twice daily), or unoprostone (0.12 to 0.15% twice daily) at reducing IOP over 1 to 12 months' treatment (table I). After 3 months of treatment, diurnal IOP was lower with latanoprost than dorzolamide ($p < 0.001$) [table I] and more patients treated with latanoprost achieved an IOP reduction of $\geq 30\%$ (52 vs 14%; p value not reported). This large study was, however, nonblind.

Latanoprost reduced IOP significantly further than brimonidine 0.2% twice daily in the two largest, albeit nonblind comparisons, both 6 months in duration,^[95,96] and in one of the small, double-blind trials^[90] when given for 6 weeks (table I). The effects of latanoprost were maintained throughout the day: for example, the percentage of patients with

Table I. Summary of prospective, randomised clinical trials comparing the intraocular pressure (IOP)-lowering efficacy of topical latanoprost (L) monotherapy with other topical pressure-lowering agents in patients with open-angle glaucoma or ocular hypertension

Reference (study design)	No. of evaluated pts ^a	Treatment regimen ^b	IOP (mm Hg; mean) ^c	
			baseline	reduction from baseline (%)
Compared with timolol (T)				
Alm & Stjernschantz ^[74]	89	L 0.005% od am x 3mo then pm x 3mo	24.8	8.6 (35)**††
(db)	94	L 0.005% od pm x 3mo then am x 3mo	25.5	7.8 (31)*
	84	T 0.5% bid x 6mo	24.6	6.7 (27)*
Aquino & Lat-Luna ^[86] (db)	28	L 0.005% od x 3mo	29.3	11.1 (39)**††
	29	T 0.5% bid x 3mo	29.3	9.1 (32)**
Camras ^[76] (db)	118	L 0.005% od x 6mo	25	6.7 (27)††
	130	T 0.5% bid x 6mo	25	4.9 (20)
Mishima et al. ^[87] (db)	80 ^d	L 0.005% od am x 3mo	23.1 ^e	6.2 (27)††
	83 ^d	T 0.5% bid am x 3mo	23.1 ^e	4.4 (19)
Watson & Stjernschantz ^[75]	86	L 0.005% od x 6mo	25.2	8.5 (34)**
(db)	79	T 0.5% bid x 6mo	25.4	8.3 (33)**
Compared with dorzolamide (D)				
O'Donoghue ^[88] (nb, mc)	109	L 0.005% od x 3mo	27.2	8.5 (31)††
	107	D 2% tid x 3mo	27.2	5.6 (21)
Compared with brimonidine (BR)				
Camras ^[96] (nb, mc)	Tot:152	L 0.005% od x 6mo	24.5	5.7 (23)††
[abstract]		BR 0.2% bid x 6mo	24.8	3.3 (13)
DuBiner et al. ^[89] (db, mc)	61 ^d	L 0.005% od x 3mo	24.1 ^e	6.5 (27)
	64 ^d	BR 0.2% bid x 3mo	24.5 ^e	6.8 (28)
Kampik et al. ^[95] (nb, mc)	187	L 0.005% od x 6mo	25.1	7.1 (28)**†††
	192	BR 0.2% bid x 6mo	24.9	5.2 (21)**
Stewart et al. ^[90] (db, co, mc)	Tot: 33	L 0.005% od x 6w	19.8	4.4 (22)**†††
		BR 0.2% bid x 6w	19.8	2.2 (11)**
Compared with bimatoprost (B)				
DuBiner et al. ^[80] (db, mc)	22	L 0.005% od x 1mo	25.2 ^e	7.6 (30)**
	21	B 0.3% od x 1mo	25.6 ^e	8 (31)**
	21	PL od x 1mo	25.8 ^e	1.7 (7)
Gandolfi et al. ^[81] (sb, mc)	113	L 0.005% od x 3mo	25.7 ^e	7.8 (30)**
	119	B 0.3% od x 3mo	25.7 ^e	8.2 (32)**
Walters et al. ^[91] (sb, mc)	38	L 0.005% od x 1mo	23.6 ^e	7.5 (32)
[poster]	38	B 0.3% od x 1mo	24.1 ^e	8.2 (34)
Compared with travoprost (TR)				
Netland et al. ^[85] (db, mc)	193	L 0.005% od x 12mo	26.9 ^e	7.5 (28)
	202	TR 0.0015% od x 12mo	26.4 ^e	7.0 (27)
	197	TR 0.004% od x 12mo	26.8 ^e	7.1 (26)
Compared with unoprostone (U)				
Aung et al. ^[77] (db, co)	Tot: 56 ^d	L 0.005% od x 1mo	22.3	6.1 (27)**†
		U 0.12% bid x 1mo	23.2	4.2 (18)**
Jampel et al. ^[94] (nb, mc)	84	L 0.005% od x 8w	25.3	7.2 (28)††
	81	U 0.15% bid x 8w	25.5	3.9 (15)

Continued next page

Table I. Contd

Reference (study design)	No. of evaluated pts ^a	Treatment regimen ^b	IOP (mm Hg; mean) ^c	
			baseline	reduction from baseline (%)
Saito et al. ^[92] (nb)	26	L 0.005% od x 6w	22.9	6 (26) ^{††}
	26	U 0.12% bid od x 6w	22.7	3.3 (15) [*]
Susanna et al. ^[93] (db)	52 ^d	L 0.005% od x 2mo	24.1	6.7 (28) ^{***††}
	53 ^d	U 0.12% bid x 2mo	24.1	3.4 (14) ^{**}

a Patients were either treatment-naïve or had withdrawn from other pressure-lowering therapy (with no more than 2 other agents) prior to the trial; the percentage of treatment-naïve versus previously treated pts was not provided except where indicated.

b L was administered as a single drop to the eye in the evening unless otherwise specified.

c IOP was calculated from the mean of 2 or 3 measurements taken between 8am and 5pm (unless otherwise indicated).

d Percentage of treatment-naïve pts was 47 and 46% of L and T groups,^[87] 77% of all pts,^[77] 14 and 15% of L and U recipients,^[93] and 48 and 39% of L and BR recipients.^[89]

e Measured in the morning before drug application (trough),^[87] between 9 and 11am,^[89] and at 8am.^[80,81,85]

bid = twice daily; **co** = crossover; **db** = double-blind; **mc** = multicentre; **mo** = months; **nb** = nonblind; **od** = once daily; **PL** = placebo; **pts** = patients; **sb** = single-blind (investigator masked); **Tot** = total number of pts; **w** = weeks; * $p < 0.05$, ** $p < 0.001$ vs baseline; † $p < 0.05$, †† $p < 0.001$ vs comparator drug.

a mean IOP reduction at 10am and 5pm was 43% at both times with latanoprost and 28% and 19% with brimonidine.^[95]

However, in the other double-blind trial^[89] a similar number of patients in either treatment group achieved the primary endpoint (IOP reduction $\geq 20\%$) after 3 months. Latanoprost appeared to be less effective than brimonidine in treatment-naïve patients in this trial ($p = 0.01$) but slightly better in previously-treated patients (at 1 month [$p = 0.03$], but not 3 months).^[89]

A meta-analysis of 9 double-blind studies which compared latanoprost or brimonidine with timolol or betaxolol, conducted between 1995 and 1999, suggests that latanoprost is superior to brimonidine in reducing IOP.^[101] The estimated absolute decrease in IOP from baseline was greater with latanoprost than with brimonidine at 3 (−8.4 vs −6.5mm Hg; $p = 0.004$) and 6 months (−8.0 vs −6.2mm Hg; $p = 0.045$).^[101]

All four nonblind or double-blind trials comparing latanoprost with unoprostone 0.15% twice daily for 1 to 2 months demonstrated superiority with latanoprost (table I).^[77,92-94] The mean IOP reduction was approximately twice as great with latanoprost as with unoprostone ($p < 0.001$) [table I], and 6–8 times as many latanoprost recipients achieved an IOP reduction $\geq 30\%$ (44 and 45% vs 6 and 8%; p values not reported) in the two largest trials.^[93,94]

Although some evidence is conflicting, latanoprost appeared to be generally as effective as bimatoprost 0.03% once daily at reducing morning IOP (table I).^[80,81,91] In two studies,^[80,81] bimatoprost tended to show a more consistent IOP-lowering effect during the day although this did not reach statistical significance at all time points.

In the largest of these studies ($n = 232$),^[81] bimatoprost and latanoprost produced statistically similar reductions in IOP at 8am (the primary endpoint) over 3 months of treatment (table I); however, the mean IOPs at 12pm and 4pm were significantly ($p < 0.05$) lower in the bimatoprost group (≈ 17.1 and ≈ 17.2 mm Hg) than the latanoprost group (≈ 18.1 and 17.9mm Hg) at the end of the study. In a clinically relevant, post hoc analysis,^[102] more patients treated with bimatoprost than latanoprost achieved a target IOP of ≤ 17 mm Hg (measured at 8am) [53% vs 43%; $p = 0.029$].

Latanoprost and bimatoprost had similar effects on mean IOP reduction at 8am and throughout the diurnal cycle in two smaller trials;^[80,91] the percentage of patients with an IOP ≤ 15 or 17mm Hg was also similar, except that more bimatoprost recipients had IOP ≤ 15 mm Hg in one trial ($p = 0.038$).^[91] However, this single-blind study is not yet fully published.

The IOP-lowering efficacy of latanoprost was generally similar to travoprost administered as a

single daily dose of 0.0015 or 0.004% in one large 12-month study (table I).^[85] Mean IOP at 8am, 10am or 4pm was similar for patients receiving latanoprost or travoprost at either dosage at study end. The percentage of patients who responded to treatment (i.e. those with a $\geq 30\%$ reduction in IOP or a final IOP of ≤ 17 mm Hg) was 49.6%, 49.3% and 54.7% for the latanoprost and travoprost 0.0015% and 0.004% groups, respectively ($p = 0.043$ for latanoprost vs travoprost 0.004%).

Interestingly, in a prospectively defined sub-analysis black patients treated with travoprost 0.004% tended to have a lower IOP than those receiving latanoprost throughout the study.^[85] When results were pooled over treatment visits at the 8am, 10am and 4pm timepoints, the mean IOP in latanoprost recipients ranged from 18.0 to 19.7mm Hg compared with 16.7 to 18.4mm Hg in travoprost 0.004% recipients ($p = 0.036$). However, this study was not powered to detect differences within this specific patient population and there were statistically significant differences in the baseline IOPs of black patients between treatment groups.^[85]

Compared with β -Blocker plus Other Agents

The IOP-lowering efficacy of latanoprost monotherapy has also been compared with that of dual therapy with timolol and dorzolamide (in nonblind trials) or pilocarpine (in single-blind trials) [table II]. In patients who had elevated IOP despite timolol therapy, switching to latanoprost was at least as effective at reducing diurnal IOP as adding dorzolamide (2% twice daily) or pilocarpine (2% three times daily) to the regimen (table II).

Mean diurnal IOP was reduced by 19 to 26% in patients receiving latanoprost,^[103-107] 17 to 21% in those receiving dual therapy with timolol and dorzolamide over 3 months^[103,105] and 19 to 20% of those given dual therapy with timolol plus pilocarpine for 6 weeks or 6 months.^[108,109] The mean reduction in diurnal IOP was significantly greater in latanoprost than in timolol plus dorzolamide recipients in 2 trials ($p < 0.005$)^[103,105] and than timolol plus pilocarpine in another.^[108]

Interestingly in one study, switching to latanoprost monotherapy was almost as effective as adding latanoprost to treatment with timolol (table II).^[108]

A large, nonblind, 6-month study has shown that in well-controlled patients with dual therapy of a β -blocker plus one other medication, switching to latanoprost monotherapy resulted in continued control of IOP.^[110]

4.1.2 Adjunctive Therapy with One Other Agent

Fixed Combination of Latanoprost and Timolol

Topical application of combination therapy may represent a more efficient drug delivery system than separate instillation of the individual constituents.^[111] Two individual topically applied drops separated by a 30-second interval will result in a 45% washout of the first drop and a consequent loss of effect. An interval of 2 minutes between first and second drop will result in a 17% loss of effect while a 5-minute interval will cause almost no washout of the initial drop. Any washout may result in a larger systemic dose which may increase the incidence of systemic adverse events.^[111]

Three double-blind, randomised studies^[112-114] have examined the IOP-lowering effect of the fixed combination of latanoprost (0.005%) and timolol (0.5%) in patients with primary open-angle glaucoma or ocular hypertension. Two studies^[112,113] recruited patients with prestudy IOP ≥ 25 mm Hg with prior therapy or ≥ 30 mm Hg without IOP-reducing medication and the third recruited patients with insufficient response to monotherapy (IOP > 20 mm Hg).^[114]

Two 6-month double-blind studies conducted in the Europe^[112] and in the US^[113] have shown that the fixed combination of latanoprost (0.005%) plus timolol (0.5%) administered once daily is significantly more effective at lowering IOP than either of the individual components as monotherapy (table III). Furthermore, at the end of the double-blind phase in both studies participants were offered the opportunity to continue treatment with the fixed combination latanoprost plus timolol in a nonblind manner. In the US study,^[113] 113 participants randomised to the fixed combination, 106 to latanoprost and 94 to timolol, continued into the nonblind phase. Diurnal

Table II. Results of prospective, randomised clinical trials comparing the intraocular pressure (IOP)-lowering efficacy of topical latanoprost (L) monotherapy versus combination therapy with topical timolol (T) and dorzolamide (D) or pilocarpine (P) in patients with elevated IOP despite previous timolol therapy

Reference (study design)	Number of evaluated pts ^a	Treatment regimen ^b	IOP (mm Hg; mean) ^c	
			baseline	reduction from baseline (%)
Compared with T + D				
Anon ^[103] (nb)	80	L 0.005% od x 3mo	23.5	6.1 (26) ^{††}
	75	T 0.5% bid + D 2% bid x 3mo	23.0	4.7 (21) [*]
Emmerich ^[104] (nb, mc)	85	L 0.005% od x 3mo	22.2	4.5 (20) [*]
	90	T 0.5% bid + D 2% bid x 3mo	22.2	4.4 (20) [*]
García Sánchez ^[105] (nb, mc)	77	L 0.005% od x 3mo	23.0	5.2 (23) ^{††}
	79	T 0.5% bid + D 2% bid x 3mo	23.7	4.0 (17) [*]
Honrubia et al. ^[107] (nb, mc)	113	L 0.005% od x 3mo	23.2	4.3 (19) [*]
	113	T 0.5% bid + D 2% bid x 3mo	23.1	4.0 (17) [*]
Polo et al. ^[106] (mc, nb)	18	L 0.005% od x 3mo	22.1	5.0 (23) [*]
	17	T 0.5% bid D 2% bid x 3mo	22.4	3.4 (18) [*]
Compared with T + P				
Bucci ^[108] (sb, mc)	46	L 0.005% od x 6mo	21.5 ^d	5.5 (25) ^{††e}
	37	T 0.05% bid + P 2% tid x 6mo	22.3 ^d	4.2 (19) [*]
	45	T 0.05% bid + L 0.005% od x 6mo	21.5 ^d	6.1 (28) [*]
Nordman et al. ^[109] (sb, mc)	102	L 0.005% od x 6w	24.3	5.4 (22) [*]
	95	T 0.5% + P 2% bid ^f x 6w	24.2	4.9 (20) [*]
Compared with β-blocker plus other agents				
Pillunat et al. ^[110] g (nb, mc)	348	L 0.005% od x 6mo	17.8	0.26
	114	β -blocker plus other agents ^h	17.6	0.37

a All patients underwent a 2- to 4-week run-in period with T before switching to L or continuing with T and adding D or P.

b L was administered as a single drop to the eye in the evening.

c IOP was calculated from mean of 3 different daily measurements taken between 8am and 4pm.

d Baseline values estimated from graph.

e Compared with timolol plus pilocarpine only.

f Fixed combination.

g At baseline, patients with well-controlled glaucoma were receiving dual therapy of β -blocker plus one other medication and had IOP ≤ 21 mm Hg.

h Adjunctive treatments to β -blocker therapy included dorzolamide, pilocarpine, brimonidine, clonidine and dipivefrine.

bid = twice-daily; **mc** = multicentre; **mo** = months; **nb** = nonblind; **od** = once-daily; **pts** = patients; **sb** = single-blind (investigator masked); **tid** = 3 times daily; **w** = weeks; * $p < 0.001$ vs baseline; † $p < 0.005$ vs comparator.

IOP levels at week 26 and 52 were 19.4 mm Hg and 18.9 mm Hg in patients randomised to the fixed combination, 20.1 mm Hg and 20.1 mm Hg in those randomised to receive latanoprost and 21.6 mm Hg and 19.3 mm Hg in those randomised to timolol.^[113] A retrospective analysis of the data from patients whose IOP was inadequately controlled during the blinded phase of the study and were switched to the fixed combination indicates that 79% of patients who switched from timolol monotherapy to the fixed combination, and 67% of those who switched

from latanoprost monotherapy achieved a ≥ 5 mm Hg reduction in IOP.^[115]

In the European study, the IOP-lowering effect of the fixed combination therapy at 26 weeks was maintained after a further 26 weeks nonblind treatment (mean diurnal IOPs were 18.5 mm Hg at week 26 and 18.2 mm Hg at week 52).^[112] The outcomes in patients who switched from monotherapy to the fixed combination therapy after 26 weeks is not reported.

Table III. Results of prospective randomised clinical trials comparing the intraocular pressure (IOP)-lowering efficacy of a fixed combination of latanoprost (L) and timolol (T) with other IOP-lowering therapies

Reference (study design)	Number of evaluated pts	Treatment regimen	IOP (mm Hg; mean)	
			baseline	reduction from baseline (%)
Compared with monotherapy L and T				
Higginbotham et al. ^[113] (db, dd, mc)	138 ^a	L 0.005% + T 0.5% od x 6mo	23.1	3.2 (14) ^{ab}
	140 ^a	L 0.005% od x 6mo	22.9	2.1 (9)
	140 ^a	T 0.5% bid x 6mo	23.7	0.3 (1)
Pfeiffer ^[112] (db, dd, mc)	140 ^a	L 0.005% + T 0.5% od x 6mo	21.6	2.6 (12)**
	147 ^a	L 0.005% od x 6mo	22.5	2.1 (9)
	149 ^a	T 0.5% bid x 6mo	22.5	1.1 (5)
Compared with combination of dorzolamide (D) and timolol				
Shin et al ^[114,116] (sb, mc)	125	L 0.005% + T 0.5% od x 3mo	27.9	9.4 (34)†
	128	D 2% + T 0.5% bid x 3mo	27.5	8.4 (30)

a All pts received timolol 0.5% bid for 2 to 4 wks prior to starting randomised study therapy.

b Least square mean difference between fixed combination and monotherapy between weeks 2 and 26.

bid = twice daily; **db** = double-blind; **dd** = double-dummy; **mc** = multicentre; **mo** = months; **od** = once daily; **pts** = patients; **sb** = single-blind (investigator-masked); * $p \leq 0.005$, ** $p < 0.001$ vs comparators and $\dagger p = 0.017$.

The fixed combination of latanoprost and timolol was significantly more effective than the fixed combination of dorzolamide and timolol in lowering IOP in a 3 month investigator-masked study. (table III).^[114,116]

Added to Timolol Therapy

The effects of adding latanoprost to another pressure-lowering agent have been investigated in several comparative studies. In these investigations, prior glaucoma therapy was either continued^[117] or was withdrawn and substituted for a baseline run-in period with timolol monotherapy.^[108,118,119]

Latanoprost was significantly more effective than pilocarpine (2% three times daily)^[108,118] and dorzolamide (2% twice daily),^[119] and as effective as brimonidine (0.2% twice daily)^[117] at reducing IOP (when assessed at peak effect) when added to existing topical β -blocker monotherapy (table IV). Mean IOP was reduced by 24 to 32% with adjunctive latanoprost (3–6 months), 19 to 21% with adjunctive pilocarpine (6 months), 20% with adjunctive dorzolamide (3 months) and 22% with adjunctive brimonidine (3 months). Latanoprost plus timolol reduced IOP by $\geq 30\%$ in approximately twice as many patients as pilocarpine plus timolol (figure 2) in two 6-month trials.^[108,118]

Clinical success ($\geq 15\%$ additional reduction in IOP after 1 months' treatment) was achieved in a similar number (81 and 82%) of patients receiving latanoprost and brimonidine with a β -blocker for 3 months.^[117]

Added to Other Antiglaucoma Medications

Latanoprost has also shown additive effects when used in combination with a range of ocular hypotensive medications including timolol (β -blocker),^[37,84,120] dipivefrine (adrenoceptor agonist),^[121] acetazolamide (oral carbonic anhydrase inhibitor),^[79] dorzolamide (topical carbonic anhydrase inhibitor)^[78] and pilocarpine (cholinergic agent)^[73,122] in a number of small ($n \leq 50$) randomised trials (table V).

Although preclinical studies in monkeys suggested that cholinergic agonists may reduce uveoscleral outflow and consequently decrease the IOP-lowering effects of prostaglandins,^[122,123] latanoprost and pilocarpine demonstrated additive effects when used in combination in two 1-week clinical trials (table V).^[73,122] Additive effects of this combination appear to be dependent on the timing and order of pilocarpine and latanoprost administration.^[124] In one study,^[124] daytime administration of pilocarpine 1 or 2% three times daily (i.e. no bedtime dose) had no significant additional effect on reduction of

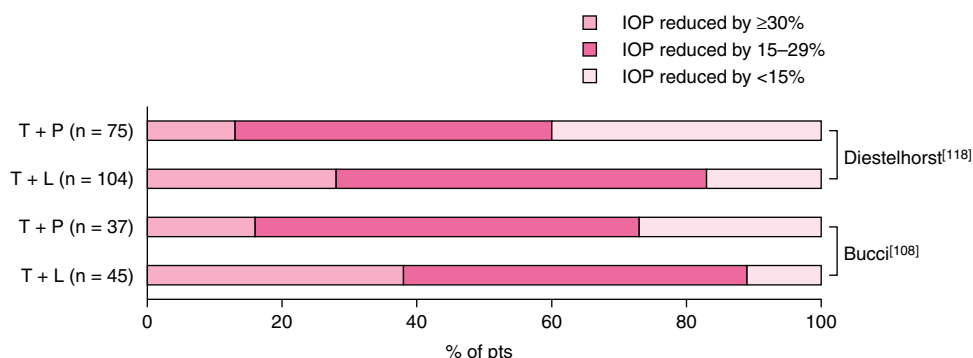


Fig. 2. The comparative effects of adding topical latanoprost (L) 0.005% once daily or pilocarpine (P) 2% twice daily to therapy with timolol (T) 0.5% twice daily: results of two 6-month randomised trials.^[108,118] Data from one study are presented according to a per-protocol analysis.^[118] IOP = intraocular pressure; pts = patients.

morning IOP when added to latanoprost therapy. However, when a fourth pilocarpine dose was given at the same time or 1 hour after the latanoprost dose, morning IOP was significantly reduced by 2 to 3mm Hg compared to baseline during latanoprost treatment ($p < 0.05$) [reductions estimated from graph]. In contrast, no significant reduction in morning IOP

was observed when the fourth dose was given simultaneously with, or 1 hour before the latanoprost dose, indicating that pilocarpine should be administered after latanoprost to achieve optimal hypotensive efficacy.^[124]

Combining latanoprost with unoprostone (the two prostaglandins that are thought to have slightly

Table IV. Results of prospective, randomised clinical trials comparing the intraocular pressure (IOP)-lowering effects of latanoprost (L) with other IOP-lowering therapies when added to monotherapy with a β -blocker

Reference (study design)	No. of evaluated pts	Baseline treatment	Added treatment ^a	IOP (mm Hg; mean) ^b	
				baseline	reduction from baseline (%)
Compared with pilocarpine (P)					
Bucci ^[108] (sb, mc)	45	T 0.5% bid 2-4 wks	L 0.005% od x 6mo	21.5 ^c	6.1 (28) ^{††}
	37		P 2% tid x 6mo	22.3 ^c	4.2 (19) [*]
Diestelhorst ^{†[118]} (nb, mc)	120 ^d	T 0.5% bid 2-4 wks	L 0.005% od x 6mo	23.3	5.6 (24) ^{††}
	120 ^d		P 2% tid x 6mo	23.0	4.8 (21) [*]
Compared with dorzolamide (D)					
Petounis et al. ^[119] (nb, mc)	73	T 0.5% bid 2-4 wks	L 0.005% od x 3mo	22.2	6.9 (32) ^{††}
	75		D 2% bid x 3mo	22.5	4.4 (20) [*]
Compared with brimonidine (BR)					
Simmons & Earl ^[117] (db, mc)	53 ^e	β-Blocker (ongoing)	L 0.005% od x 3mo	21.3 ^f	5.5 (25)
	54		BR 0.2% bid x 3mo	21.4 ^f	4.6 (22)

a L was administered as a single drop to the eye in the evening.

b IOP was calculated from mean of three different daily measurements taken between 8am and 4pm (unless otherwise indicated).

c Baseline estimated from graph.

d Intent-to-treat analysis; 4 pts receiving L and 35 receiving P did not complete the study ($p < 0.001$).

e Only pts who achieved a $\geq 15\%$ reduction in IOP after 1 month of treatment were included in the 3-month IOP analysis (43 of 53 patients receiving L and 44 of 54 pts receiving BR).

f Measured at 10am (peak drug effect for both L and BR).

bid = twice daily; db = double-blind; mc = multicentre; mo = months; nb = nonblind; od = once daily; pts = patients; sb = single-blind (investigator masked); tid = 3 times daily; * $p < 0.001$ vs baseline; † $p < 0.001$ vs comparator.

Table V. Results of prospective, randomised clinical trials investigating the intraocular pressure (IOP)-lowering efficacy of latanoprost (L) when used in combination with other anti-glaucoma agents in patients with open-angle glaucoma

Reference (study design)	No. of evaluated pts	Monotherapy ^a	Added treatment ^b	IOP (mm Hg; mean) ^c			
				baseline	on monotherapy	on combination therapy	difference between monotherapy and combination therapy (%)
Timolol (T) combination							
Alm et al. ^[37]	25	T 0.5% bid (ongoing)	L 0.006% od x 12w	24.8	-	15.7	9.1 (37)
(db, mc)	25	T 0.5% bid (ongoing)	L 0.006% bid x 12w	24.9	-	18	6.8 (28) [†]
Bron et al. ^[84]	17	T 0.5% od x 2w	L 0.005% od x 6w	NR	23.2 ^d	17.5 ^d	5.7 (25)**
(db, mc)	16	T 0.5% od x 2w	T monotherapy continued x 6w	NR	24.2 ^d	23.8 ^d	0.4 (2)
Rulo et al. ^[120]	10	L 0.006% bid x 1w	T 0.5% bid x 1w	28.5	19.6	17	2.6 (14)*
(sb)	10	T 0.5% bid x 1w	L 0.006% bid x 1w	24.2	18.3	15.7	2.6 (13)*
Acetazolamide (A) combination							
Rulo et al. ^[79]	12	A 250mg bid x 3d	L 0.005% od x 2wk	25.4	19.5	16.8	2.9 (15)**
(db)	12	A 250mg bid x 3d	PL od x 2w	26.1	21.5	22.8	↑1.3 (↑6)**
Dorzolamide (D) combination							
Kimal Arici et al. ^[78]	15	L 0.005% od x 10d	D 2% tid x 10d	26.8	18.7	15.9	2.8 (15)*
(sb)	15	D 2% tid x 10d	L 0.005% od x 10d	26.3	21.2	16.1	5.1 (24)*
Dipivefrine (DIP) combination							
Watson et al. ^[126]	10	L 0.006% bid x 1w	DIP 0.1% bid x 1w	24.7	16.9	14.7	2.2 (13)*
(sb)	10	DIP 0.1% bid x 1w	L 0.006% bid x 1w	26.3	19.1	13.8	5.3 (28)*
Widengård et al. ^[121]	11	L 0.005% od x 2w	DIP 1 mg/ml bid x 2w	19.3	14.8	12.4 ^d	2.3 (16)*
(nb)	11	DIP 1 mg/ml bid x 2w	L 0.005% od x 2w	22.3	18.4	14.9 ^d	3.5 (19)**
Pilocarpine (P) combination							
Fristrom & Nilsson ^[73]	10	P 2% tid x 1w	L 0.006% bid x 1w	23.8	20.4	17.7	2.7 (14)*
(sb)	10	L 0.006% bid x 1w	P 2% tid x 1w	25.1	19.1	17.6	1.5 (7)*
Toris et al. ^[122]	Tot: 30 ^e	L 0.005% od x 1w	P 2% qid ^f x 1w	17.6	14.3	12.7 ^g	1.6 (15)*
(db, co)		P 2% qid x 1w	L 0.005% od x 1w	18.9	16.2	13.7 ^g	3.3 (11)**
Unoprostone (U) combination							
Aung et al. ^[127]	15	L 0.005% od x 4w	U 0.12% bid x 4w	24.4	17.8	18.2	↑0.4 (↑2)
(sb)	17	U 0.12% bid x 4w	L 0.005% od x 4w	24.4	19.6	18.0	1.9 (10)*

Continued next page

Table V. Contd

Reference (study design)	No. of evaluated pts	Monotherapy ^a	Added treatment ^b	IOP (mm Hg; mean) ^c			difference between monotherapy and combination therapy (%)
				baseline	on monotherapy	on combination therapy	
Saito et al. ^[92]	26	L 0.005% od x 6w	U 0.12% bid x 6w	22.9	16.9	16.7	0.2 (1)
(nb)	26	U 0.12% bid x 6w	L 0.005% od x 6w	22.7	19.4	16.8	2.6 (13)*
a All agents were given topically except for acetazolamide (oral).							
b L was administered as a single drop to the eye in the evening.							
c Mean of two or three recordings taken at different times of day between 8am and 5pm (unless otherwise indicated).							
d Recorded at 9am.							
e 3-week washout between treatments.							
f Fourth P dose given 5 minutes before L.							
g Measured at peak P effect (10.45am).							
bid = twice daily; co = crossover; db = double-blind; mc = multicentre; mo = months; nb = nonblind; NR = not reported; od = once daily; PL = placebo; pts = patients; qid = 4 times daily; sb = single-blind (investigator masked); Tot = total number of patients; tid = 3 times daily; w = weeks; * p < 0.01, ** p < 0.001 vs monotherapy; † p < 0.01 vs L od; ‡ indicates increase.							

differing mechanisms of action) significantly reduced IOP when latanoprost was added to unoprostone therapy, but not *visa versa* (table V).^[92] In fact, the IOP reduction obtained with adding unoprostone to latanoprost did not exceed that obtained with latanoprost therapy alone, indicating that an additive effect with this combination is unlikely.^[92]

A retrospective analysis has suggested that dorzolamide is the most effective adjunctive treatment in patients whose glaucoma was inadequately controlled by latanoprost alone.^[125] In a total of 73 patients with glaucoma, addition of dorzolamide to latanoprost treatment further reduced IOP by 3.9mm Hg, while β -blockers and brimonidine each further reduced IOP by 2.0mm Hg.

4.1.3 Adjunctive Therapy with At Least Two Other Agents

The IOP-lowering effects of latanoprost have been investigated in patients receiving multiple medications or on maximally tolerated medical therapy in a small number of prospective clinical trials.

Across these single-blind^[128] and noncomparative trials,^[129-131] latanoprost produced an additional 16 to 18% reduction in IOP when added to existing therapy (table VI). Effect on IOP or response rate (table VI) did not differ significantly between latanoprost and brimonidine 0.2% twice daily after 1 months' treatment in the only randomised trial.^[128] Reductions in IOP with the two drugs were similar whether patients were receiving concomitant pilocarpine or dorzolamide plus a β -blocker.^[128]

The additional reduction with latanoprost was evident after 1 week of therapy in a noncomparative trial.^[129] In patients already receiving maximally tolerated IOP-lowering therapy with various drugs, the response rate (percentage of patients achieving an IOP reduction >20%) at 1 month was 44% in the largest trial.^[130] This rate was higher (70%) at 1 month in a separate, smaller investigation, but declined to around 40% at 3 and 6 months and to 30% at the end of the 12-month study.^[131]

4.2 Angle-Closure Glaucoma

The primary management of patients with angle-closure glaucoma is a peripheral iridotomy to re-

Table VI. Efficacy of latanoprost (L) as adjunctive therapy with ≥ two other agents in prospective studies conducted in patients with open-angle glaucoma

Reference (study design)	No. of evaluated pts	Baseline therapy	Added treatment	IOP (mm Hg) ^a		Response rate (%) ^b
				baseline	reduction (%)	
Patelska et al. ^[100]	160	Various	L 0.005% od x 1mo	23.3	4.1 (18)*	44
Shin et al. ^[131]	61	Various	L 0.005% od x 12mo	23.5	3.9 (17)***	1mo: 70; 12mo: 30
Simmons & Samuelson ^[128] (r, sb, mc)	20	β-Blocker + D or P	L 0.005% od x 1mo	NR	3.43 (17)**	65
	20		B 0.2% bid x 1mo	NR	4.6 (23)**	85
Susanna et al. ^[129]	47	T 0.5% + D 2%	L 0.005% od x 1mo	19.3	3.1 (16)***	36

a Where stated, this was measured at peak effect.

b Percentage of pts achieving a >15%^[128] or ≥20%^[129-131] reduction in IOP.

B = brimonidine; **bid** = twice daily; **D** = dorzolamide; **IOP** = intraocular pressure; **mc** = multicentre; **mo** = months; **NR** = not reported; **od** = once daily; **P** = pilocarpine; **pts** = patients; **r** = randomised; **sb** = single-blind (investigator masked); **T** = timolol; * $p < 0.01$, ** $p < 0.001$, *** $p < 0.0002$ vs baseline.

move pupillary block;^[4,132] however, many patients continue to have elevated IOP following iridotomy and are candidates for topical IOP-lowering treatment. If patients fail to respond to medical treatment, surgical iridectomy or trabeculectomy is indicated.^[4,132]

The efficacy of latanoprost has been investigated in a few studies that included patients of Asian descent who had elevated IOP despite iridotomy and/or iridectomy (table VII).^[133-135] All patients were receiving IOP-lowering drugs before trial enrolment; these were either withdrawn in the randomised double-blind monotherapy trials or continued in the adjunctive noncomparative trial before initiation of latanoprost therapy.

Latanoprost reduced IOP further than timolol 0.5% at 2^[133] and 12 weeks^[134] in available monotherapy trials; both drugs decreased IOP from baseline (table VII). The larger of the two trials, reported as an abstract, included patients with chronic angle-closure glaucoma defined as the presence of at least 180 degrees of appositional angle closure, peripheral anterior synechiae and optic neuropathy/visual field loss.^[134] In the other study,^[133] patients had bilateral or unilateral angle-closure glaucoma, defined as >6 clock hours of synechial angle closure on gonioscopy, optic neuropathy and visual field loss. Although more patients in the latanoprost than the timolol group had an angle closure of 6 to 9 clock hours (n = 16 vs 10), the degree of angle closure did not affect the extent of IOP reduction, nor did previous medication influence the response.^[133]

As adjunctive therapy in a small nonblind trial, latanoprost rapidly decreased mean IOP; the reduction was significant by the end of week 1 (21%, $p < 0.005$). The decrease persisted through 3 months of therapy and, in the eight patients treated for a year, was about 36% from baseline (table VII).^[135] All patients had undergone iridectomy and were receiving combined treatment with β-blockers and pilocarpine with (n = 14) or without (n = 12) oral carbonic anhydrase inhibitors. Laser peripheral iridoplasty had also been performed in 19 eyes. Results of this small study suggest that that latanoprost has an

Table VII. Efficacy of latanoprost (L) as monotherapy or adjunctive therapy in patients with angle-closure glaucoma in prospective trials

Reference (study design)	No. of evaluated pts	Treatment ^a	IOP (mm Hg)	
			baseline	reduction from baseline (%)
As monotherapy				
Aung et al. ^[133] (r, db)	32 in total	L x 2w	25.7	8.8 (34%)*†
		T 0.5% bid x 2w	25.2	5.7 (23)*
Chew ^[134] (r, db) [abstract]	275 in total	L x 12w	NR	8.2** ^b
		T 0.5% bid x 12w	NR	5.2*
As adjunctive therapy^c				
Hung et al. ^[135] (nb)	26	L x 3mo	23.2	5.9 (25)**
	8 (of the above 26)	L x 1y		8.9 (36)**

a L dosage was 0.005% as a single drop once daily.

b No p value was given; 95% CI: 2.1, 4.0.

c L was added to unidentified existing therapy.

bid = twice daily; **db** = double-blind; **IOP** = intraocular pressure; **mo** = months; **nb** = nonblind; **NR** = not reported; **pts** = patients; **r** = randomised; **T** = timolol; **w** = weeks; **y** = years; * $p < 0.001$ vs baseline, ** $p < 0.005$; † $p = 0.04$ vs T.

additional effect in patients who would otherwise be candidates for further surgical intervention.^[135]

4.3 Other Types of Glaucoma

A few small ($n \leq 36$) studies have investigated the potential role of latanoprost in the treatment of other specific types of glaucoma including normal-tension glaucoma,^[64,65,136,137] pigmentary glaucoma,^[138] steroid-induced glaucoma^[139,140] and glaucoma associated with Sturge-Weber syndrome (SWS).^[141,142] A few have compared latanoprost with timolol in various indications in randomised trials (table VIII).

In these trials, latanoprost had similar efficacy to timolol in patients with normal-tension and steroid-induced glaucoma after 3 weeks^[65] and 4 months,^[139] respectively, and produced significantly

greater reductions in IOP than timolol in patients with pigmentary glaucoma after 12 months' therapy (table VIII).^[138] In the latter patients,^[138] the diurnal IOP curve showed a much flatter profile with latanoprost than with timolol, reflecting fewer diurnal fluctuations. The authors suggested that the increased uveoscleral outflow induced by latanoprost (section 2) may permit increased pigmentary clearance and reduced IOP spikes.^[138] However, results of these trials require confirmation in larger well-designed studies.

Some further support for the efficacy of latanoprost in some of these indications is nevertheless available from small noncomparative trials.^[64,136,140-142] Reductions in IOP were similar to those in the randomised trial ($\approx 21\%$ $p < 0.001$ vs baseline in both studies) in two noncomparative

Table VIII. Efficacy of latanoprost (L) versus timolol (T) in randomised trials conducted in patients with various types of glaucoma.

Reference (study design)	No. of evaluated pts (disease type)	Treatment ^a	IOP (mm Hg)	
			baseline	reduction from baseline (%)
Drance et al. ^[65] (db, co)	36 in total (normal tension)	L x 3w	15.4	3.6* (23)
		T 0.5% bid x 3w	15.3	3.2* (20)
Mastropasqua et al. ^[138] (db)	36 in total (pigmentary)	L x 12mo	≈ 24	5.9*†
		T 0.5% bid x 12mo	≈ 24	4.6*
Vetrugno et al. ^[139] (nb)	29 in total (steroid-induced)	L x 4mo	25.1	10.4 (41)
		T 0.5% bid x 4mo	24.7	9.6 (39)

a L dosage was 0.005% as a single drop once daily.

bid = twice daily; **co** = crossover; **db** = double-blind; **IOP** = intraocular pressure; **mo** = months; **nb** = nonblind; **pts** = patients; **w** = weeks; * $p < 0.001$; † $p < 0.001$ vs T.

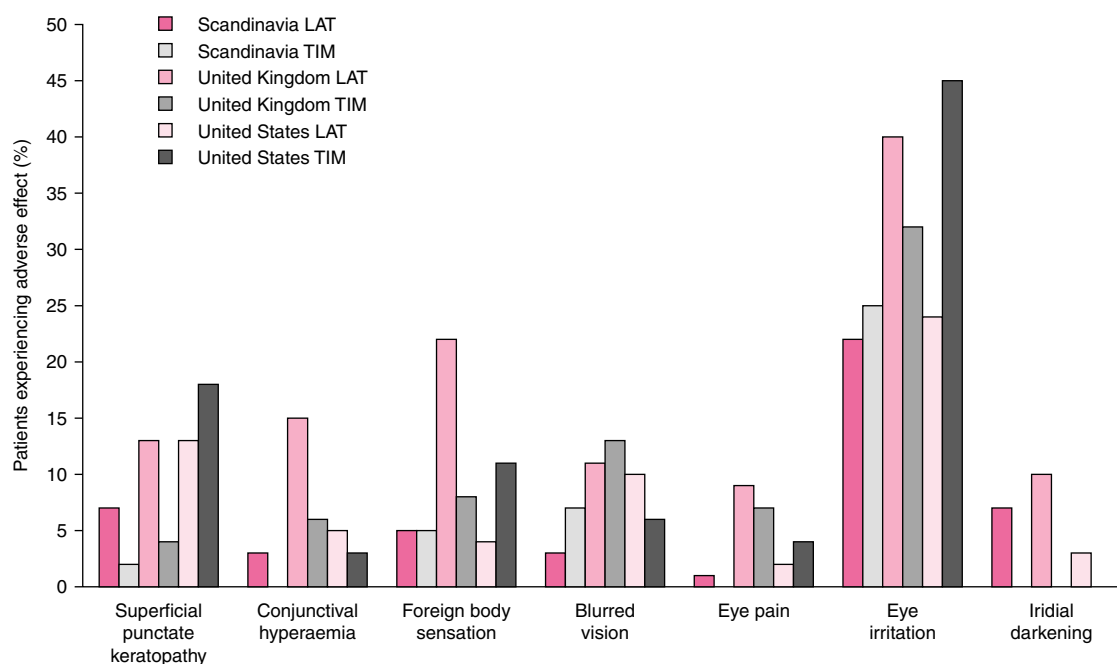


Fig. 3. Percentage of patients experiencing ocular signs and symptoms during topical treatment with either latanoprost (LAT) or timolol (TIM). Patients were randomised to receive either LAT 0.005% once daily or TIM 0.5% twice daily in three double-blind, multicentre phase III studies carried out in the United Kingdom (n = 294), United States (n = 268) and Scandinavia (n = 267).^[143] Patients received treatment for 6 months and had raised intraocular pressure at study entry. Statistical analyses not available.

trials including patients with normal-tension glaucoma (n = 19 and 30) receiving latanoprost for 3 to 4 weeks.^[64,136] As well, latanoprost reduced mean IOP by 28% (p < 0.005 vs baseline) in all eyes of eight patients with newly diagnosed steroid-induced glaucoma.^[140] The drug has, however, shown only modest efficacy in SWS-induced glaucoma in two small studies.^[141,142]

5. Tolerability

The tolerability of latanoprost in patients with glaucoma and ocular hypertension has been previously reviewed in *Drugs & Aging*.^[11] Briefly, data from phase III trials showed that topical latanoprost was generally well tolerated, with an ocular tolerability profile similar to that of timolol (although incidence of individual adverse events did differ between treatments; see figure 3).^[11,143] Conjunctival hyperaemia was not observed or showed a barely detectable increase in $\geq 90\%$ of patients receiving either drug;^[11] 3 to 10% of patients showed iridial

pigmentation after 3 to 4.5 months' continuous treatment with latanoprost.^[11] In contrast to timolol, latanoprost therapy was associated with minimal systemic adverse events.^[11] More recently latanoprost has shown acceptable tolerability when used in combination with other glaucoma medications including timolol,^[84] dorzolamide,^[84] dipivefrine,^[121] pilocarpine,^[124] and acetazolamide.^[79] The incidence of adverse events increased predictably according to the tolerability profile of the concomitant therapies.

This section focuses on data from recent trials which have compared once-daily latanoprost therapy with either bimatoprost 0.3%^[80,81] or travoprost 0.0015 and 0.004%^[85] (all once daily) or dorzolamide 2%,^[88] brimonidine 0.2%^[90,95] or unoprostone 0.12 or 0.15% (all twice daily) [section 4.1].^[77,93,94]

Overall, adverse events associated with latanoprost therapy are mild and reversible upon discontinuation of treatment. A similar incidence of both

ocular and systemic adverse events has been observed in short-term studies (range 30 days to 8 weeks) comparing latanoprost with bimatoprost^[80] or unoprostone,^[77,93] although in one study unoprostone recipients experienced more frequent adverse events than latanoprost recipients.^[94] However, Gandolfi et al.^[81] reported significantly more frequent conjunctive hyperaemia and increased eyelash growth in patients who received bimatoprost than in those receiving latanoprost for 3 months, whereas headache was more frequent in latanoprost than bimatoprost patients. Latanoprost has also shown a similar incidence of total adverse events to both dorzolamide and brimonidine; systemic events such as taste perversion and gastrointestinal disorders were more pronounced with dorzolamide.^[88]

In two large, double-blind randomised trials the adverse event profile associated with the fixed combination of latanoprost 0.005% and timolol 0.5% was similar to that reported for each of the individual components when administered as a monotherapy treatment (section 4.1.2).^[112,113] In a 3-month, evaluator-blind study significantly fewer patients receiving the fixed combination of latanoprost/timolol reported eye pain or any systemic adverse event than those receiving dorzolamide/timolol (4.0 vs 14.1%, $p = 0.007$ and 13.6 vs 23.4%, $p = 0.044$).^[114]

5.1 Ocular Adverse Events

Overall, ocular events observed in patients with glaucoma who received latanoprost were mild to moderate in severity and resolved after discontinuation of treatment.

5.1.1 Conjunctival Hyperaemia

Conjunctival hyperaemia is a common adverse event of topical prostaglandin treatment.^[144] It usually occurs within the first 2 days after initiation of latanoprost treatment, diminishes with time (after 2 to 4 weeks) and is mild in the majority of patients.^[11]

The incidence of conjunctival hyperaemia with latanoprost was similar to that of bimatoprost in a 1-month trial (14% for both)^[80] but was lower in a 3-month trial (14 vs 36%, $p \leq 0.001$); this was mild in $\approx 95\%$ of patients in both groups.^[81] Compared with brimonidine twice daily, latanoprost was asso-

ciated with a higher incidence of this adverse event in a 6-week trial (36 vs 9%)^[90] and a similar incidence after 6 months (6%).^[95] Conjunctival hyperaemia was observed in 27.6, 38, 49.5 and 14.0% of patients given latanoprost, travoprost (0.0015 or 0.004%) or timolol for 12 months.^[85]

5.1.2 Iris Pigmentation

Increased iris pigmentation has been reported in 5 to 25% of patients with glaucoma treated with latanoprost.^[145] This usually occurs in mixed-colour eyes (i.e. blue-brown, green-brown, yellow-brown and grey-brown), but rarely in blue, green, grey or brown eyes,^[144] and may appear as soon as 3 months after initiation of therapy.^[100] Iris freckles or naevi are not affected.^[144] The pathogenesis of iridial darkening is not completely understood, but it may be a result of a prostaglandin-stimulated increase in melanin production.^[145,146] After cessation of latanoprost treatment, increased pigmentation persisted in patients followed for 2 years.^[145]

Darkening of the irises was not seen in one report of 317 Japanese patients with glaucoma and predominantly brown eyes who received latanoprost for approximately 4 months.^[147] However, in a prospective, blinded study in 69 Japanese patients with glaucoma, iridial darkening increased with continued treatment (seen in 3.5, 9.7 and 35.0% of eyes after 1, 3 and 6 months).^[148] In a comparative study, one patient receiving latanoprost (0.005%) and no patients receiving brimonidine experienced an increase in iris pigmentation.^[95]

5.1.3 Hypertrichosis and Hyperpigmentation

Several effects on eyelid lashes (particularly the lower lashes) have been noted following treatment with latanoprost, including an increase in the length, number, colour and thickness.^[149,150] Hypertrichosis of the upper and/or lower eyelids was reported in 77% and eyelid discolouration in 40% of 317 Japanese patients with glaucoma who received latanoprost for approximately 4 months.^[147] However, eyelash growth occurred 3-fold more often in patients who received once-daily bimatoprost compared with latanoprost in a randomised 3-month study (12.6 vs 4.4%; $p = 0.026$).^[81] In a 6-month study, hypertrichosis was reported by 3.2% of pa-

tients receiving latanoprost, and none of those receiving brimonidine.^[95]

Additionally, a recent case report has detailed hyperpigmentation of the periocular skin following treatment with latanoprost, which resolved after discontinuation of the drug.^[151] Fewer than 40 reports of hyperpigmentation (primarily in the eyelid and periocular regions) during latanoprost treatment have been collected by the Worldwide Adverse Experience System (WAES); patients were mostly female and aged 47 to 80 years.^[151] Thirteen reports of periocular hyperpigmentation have also been forwarded to the National Registry of Drug-Induced Ocular Side Effects (NRDIOSE).^[151] It is likely that increased awareness of periocular hyperpigmentation as a potential adverse event associated with latanoprost treatment will reveal a greater prevalence of the condition than was previously thought.

An increase in the severity and recurrence of herpes simplex virus keratitis has been reported in five patients (age ≥ 65 years) after initiation of latanoprost therapy^[152,153] and caution is advised in patients with a history of herpes in the manufacturer's prescribing information.^[71] Herpetic dermatitis of the periocular skin associated with latanoprost therapy has also been reported in two patients aged 79 and 84 years.^[154]

5.1.4 Cystoid Macular Oedema and Uveitis

Previous surgery or a history of intraocular inflammation may predispose some patients with glaucoma who receive latanoprost to cystoid macular oedema or uveitis.

Although the incidence of cystoid macular oedema was low in clinical trials,^[11,143] post-marketing experience has revealed several cases of cystoid macular oedema in aphakic^[155,156] as well as pseudophakic eyes.^[156-162] In recent reviews of case reports ($n = 25$ and 9) by Schumer et al.^[163] and Moroi et al.^[164] and a retrospective review of 94 patients treated with latanoprost,^[165] all eyes that developed cystoid macular oedema had independent risk factors for the condition, such as posterior lens capsule rupture or macular traction.^[165]

Anterior uveitis has also been observed in approximately 1% of patients receiving latanoprost

and is resolved with corticosteroid therapy.^[166] Administration of latanoprost to patients with active uveitis at the time of treatment may or may not aggravate the condition, but does not appear to lower IOP.^[166,167] However, two studies involving a total of ten patients showed the development of uveitis after initiation of latanoprost treatment, which was resolved after discontinuation of treatment but recurred with rechallenge.^[165,168]

5.1.5 Other Ocular Events

Additionally, the development of dendritiform epitheliopathy (corneal lesions) has been observed in four patients (aged ≥ 63 years) with glaucoma (two of whom also had diabetes mellitus) following latanoprost therapy. Clinical symptoms resolved after the drug was discontinued.^[169]

5.2 Systemic Adverse Events

Topically administered drugs undergo systemic absorption through the nasopharyngeal mucosa after ocular administration.^[170] However, latanoprost-related systemic adverse events are infrequently seen because the drug and its metabolites have a relatively rapid elimination half-life (section 3).

5.2.1 Respiratory

Elderly patients, in particular, have higher rates of both glaucoma and obstructive airway disease than younger patients, and obstructive airway disease can be aggravated by β -blocker treatment for glaucoma.^[170] PGD_2 and $\text{PGF}_{2\alpha}$ may induce thromboxane-mediated bronchoconstrictive effects in the lung. However, effects related to pulmonary function are unlikely with latanoprost as it is a relatively selective $\text{PGF}_{2\alpha}$ receptor agonist with minimal effects on the thromboxane receptor (section 2).^[144]

No significant effects were observed on peak expiratory flow (PEF) measurements, asthma symptoms or requirement for asthma drugs in patients with asthma (not receiving corticosteroids) treated with latanoprost in a randomised, double-blind, placebo-controlled, crossover study.^[170] Similarly, no effect was observed on spirometric measurements [PEF, forced expiratory volume in 1 second (FEV_1)

and FEV₁/forced ventilatory capacity (FVC)] in 33 patients with newly diagnosed glaucoma who received latanoprost for 3 months in a prospective comparative study (ages not specified).^[171] In contrast, both betaxolol and timolol decreased peak flow and FEV₁/FVC from baseline; shortness of breath was reported in patients treated with betaxolol (3%), brimonidine (15%) or timolol (15%), but not latanoprost.^[171]

In a 6-month clinical study, 2% (4 out of 187) of patients receiving latanoprost and 2% (4 out of 188) of those receiving brimonidine reported adverse respiratory effects. Only one of these events, in a patient receiving brimonidine, was categorised as a serious adverse event (hospitalisation due to severe bronchitis).^[95]

Four adverse respiratory tract reactions to latanoprost therapy have been reported to the Swedish Adverse Drug Reactions Advisory Committee. Deterioration of asthma was observed in three patients with pre-existing asthma (one of whom had received previous β -blocker treatment for glaucoma) and was ameliorated following discontinuation of latanoprost therapy.^[172] In one patient without previously diagnosed asthma (who had also received previous treatment with pergolide and bromocriptine), severe apnoea occurred 30 minutes after administration of latanoprost; symptoms disappeared within 1 hour.^[172]

5.2.2 Other Systemic Adverse Events

Upper respiratory tract infection/cold/flu were the most common systemic adverse events observed in clinical trials and occurred at a rate of approximately 4%.^[71] Other systemic events, each with an incidence of 1 to 2%, included chest pain/angina, muscle/join/back pain and rash/allergic skin reaction.^[71]

Angina,^[173] arterial hypertension^[174,175] and tachycardia^[174] have been anecdotally reported following initiation of latanoprost therapy in patients with glaucoma. In addition, three patients with open-angle glaucoma and no prior history of migraine and/or headache (aged ≥ 54 years) reported migraine after receiving latanoprost treatment.^[176] In a randomised study, headache was more frequent

in patients receiving latanoprost than in those receiving bimatoprost (4.4 vs 0%) although this difference did not reach statistical significance.^[81]

6. Medication Persistency

Three retrospective studies of US managed care or pharmacy claims data have assessed medication persistency (rates of discontinuation and/or change in therapy) in treatment-naïve patients with glaucoma receiving monotherapy.^[177-179] A total of 4619 patients met the eligibility criteria for these studies and were included in the final analyses. Latanoprost (24 to 33%), timolol (20 to 54%) and brimonidine (10 to 13%) were the most frequently prescribed medications.

In two of these analyses,^[177,179] patients receiving latanoprost were significantly less likely to discontinue medication than those receiving timolol (RR = 1.36, 95% CI = 1.28, 1.43) or brimonidine (RR = 1.54, 95% CI = 1.44, 1.63).^[179] Among those patients who did discontinue their medication, latanoprost recipients had a significantly longer duration of therapy (216.5 days) than recipients of timolol (183.4 days, $p < 0.001$) or brimonidine (184.2 days, $p < 0.001$).^[177] In the third analysis,^[178] discontinuation rates of patients receiving latanoprost were compared with those receiving β -blockers or carbonic anhydrase inhibitors. Of the 1330 patients included in this analysis, 59% received β -blockers, 24% received latanoprost and 13% received brimonidine. After 1 year, fewer patients receiving latanoprost discontinued or changed their glaucoma therapy (36%) compared to those receiving β -blockers (41%), carbonic anhydrase inhibitors (57%) or brimonidine (63%). Patients receiving β -blockers, carbonic anhydrase inhibitors, and brimonidine were 24, 122 and 141% more likely to discontinue or change therapy compared to patients receiving latanoprost.^[178]

7. Dosage and Administration

In the US,^[71] Europe^[180] and Japan^[181] latanoprost is approved for both first-line use in patients with open-angle glaucoma or ocular hypertension.

Latanoprost is provided as an isotonic, buffered aqueous solution which contains 0.005% latanoprost (50 µg/mL).^[71] A single drop of latanoprost 0.005% (about 1.5µg) once daily is the recommended dosage.^[71] Latanoprost can also be used in combination with other topical hypotensive agents, but the drugs should be administered at least 5 minutes apart.^[71]

Contraindications include known hypersensitivity to latanoprost, benzalkonium chloride or any other ingredients. The drug has not been adequately evaluated in patients with renal or hepatic impairment so should be used cautiously in these individuals. Latanoprost should also be used with caution in patients with active intraocular inflammation (e.g. iritis, uveitis). Contact lenses should be removed before administration of latanoprost as they may absorb benzalkonium chloride contained in the latanoprost solution; lenses may be replaced 15 minutes after application.

8. Place of Latanoprost in the Management of Patients with Glaucoma or Ocular Hypertension

Glaucoma is not a curable disease, but early detection and intervention can prevent the development of ocular complications and help preserve visual function. Treatments are aimed at reducing IOP by either reducing the amount of aqueous humour production or increasing its outflow through the trabecular meshwork, the uveoscleral pathway or a surgically created route.^[3,4] There is currently no proven direct treatment for the optic neuropathy of glaucoma.

As discussed in section 1, the factors contributing to elevated IOP in patients with open-angle glaucoma and angle-closure differ, and so too does the management of these patients; these two glaucoma variants will be discussed separately below.

8.1 Open-Angle Glaucoma or Ocular Hypertension

Open-angle glaucoma accounts for over 70% of adult glaucoma cases in Westernised countries and is estimated to affect approximately 1.6 million

Americans aged 40 years or older.^[3,5] It is estimated that an additional 7 to 8 million Americans over the age of 40 years have ocular hypertension.^[3] The risk of open-angle glaucoma is particularly high in African-American populations.^[5] For example, in one US study, the prevalence of open-angle glaucoma in persons aged over 40 years was 1.7% in Caucasians compared with 5.6% in African Americans.^[5]

The main goals of therapy in patients with open-angle glaucoma are to halt optic neuropathy and preserve visual function.^[3,10,132]

Of the numerous demographic and physiological risk factors for the development of primary open-angle glaucoma, elevated IOP is most consistently associated with the development of visual loss which becomes more frequent with further increases in IOP.^[8] Even in normal-tension glaucoma, the level of IOP is a risk factor for glaucomatous damage.^[182,183]

IOP is also the only risk factor currently amenable to treatment. A number of studies have demonstrated that reducing IOP protects against additional damage to the optic nerve head,^[184-186] even in patients with normal-tension glaucoma,^[183,187] and lowering IOP in patients with ocular hypertension may also reduce the incidence of glaucoma.^[186] US guidelines recommend a minimum IOP reduction of 20 to 30% from baseline,^[132] but some patients may require greater reductions.

First-line treatment option in the management of open-angle glaucoma is drug therapy, proceeding to laser therapy and surgery when necessary.^[3,10,132] Topical ocular hypotensive agents are currently the mainstay of pharmacological therapy, and oral carbonic anhydrase inhibitors are generally reserved for patients who are unresponsive to these agents. Until recently, β -blockers (e.g. timolol), which reduce IOP by decreasing aqueous humour production, were the usual first-line treatment option;^[3,10,132] however, latanoprost has also recently received marketing approval from the US FDA for first-line use in patients with ocular hypertension and most common forms of glaucoma.^[188] If response is insufficient, or if patients are not able to tolerate these agents, then another class of drug is

added or substituted. Currently four main classes of topical hypotensive agents are available for second-line treatment: α -agonists [e.g. dipivefrine (non-selective) and brimonidine (α_2 -selective)], parasympathomimetic agents (e.g. pilocarpine), topical carbonic anhydrase inhibitors (e.g. dorzolamide) and the prostaglandin analogues (e.g. travoprost and unoprostone).^[3,10,132] These prostaglandin analogues, including latanoprost, reduce IOP by increasing uveoscleral outflow, possibly by reducing the extracellular matrix in the spaces among ciliary muscle fibres (section 2.1).

Topical latanoprost has shown pronounced IOP-lowering efficacy in numerous clinical trials (section 4.1). In large, well-controlled trials, latanoprost 0.005% once daily reduced mean IOP by 22 to 39% over 3 or 6 months of treatment. Latanoprost was significantly more effective than timolol, dorzolamide, brimonidine and unoprostone and was generally as effective as bimatoprost and travoprost (section 4.1.1). Furthermore, in patients whose IOP was poorly controlled with timolol, switching to latanoprost monotherapy was at least as effective at lowering IOP as adding dorzolamide or pilocarpine to timolol therapy (section 4.1.1). These latter results suggest that switching to latanoprost may delay the need for combination drug therapy. This is potentially beneficial since polypharmacy can increase adverse effects and costs while reducing convenience and thus compliance.^[189]

The efficacy of latanoprost appears to be sustained during long-term treatment: IOP did not increase in patients receiving the drug for 1 or 2 years (section 4.1.1). This finding is in contrast to therapy with β -blockers, such as timolol, which have been shown to lose their hypotensive efficacy over time.^[190] The efficacy and tolerability of latanoprost in patients receiving the drug for >2 years has not yet been established.

Due to the unique mechanism of action of the prostaglandin analogues, latanoprost is also a useful adjunctive therapy. The fixed combination of latanoprost plus timolol once daily is more effective than either of its individual components when given as monotherapy and more effective than the fixed

combination of dorzolamide and timolol twice daily. Latanoprost has additive effects when combined with a range of hypotensive agents including timolol, acetazolamide, dorzolamide, dipivefrine and pilocarpine (section 4.1). Furthermore, it was more effective than pilocarpine and dorzolamide and as effective as brimonidine when added to an existing regimen of β -blocker monotherapy (section 4.1.2). The comparative efficacy of latanoprost and newer agents such as bimatoprost as adjunctive therapy has not yet been investigated.

One of the advantages of latanoprost is its long duration of action (section 2.2). This means that latanoprost can be administered once daily, which is in contrast to most other topical IOP-lowering medications which require at least twice daily instillation.^[3] This feature is likely to improve patient compliance, an important consideration considering the chronic nature of the disease and the requirement for long-term treatment.

A single daily dosage of latanoprost provides 24-hour IOP control,^[35] with similar efficacy during daytime and night-time hours.^[31,32,83] In contrast, some β -blockers, including timolol, do not effectively reduce aqueous humour production,^[191] or IOP,^[83] during night-time hours. The ability for latanoprost to maintain a relatively uniform 24-hour IOP control may be important, as it is now recognised that large fluctuations in IOP can increase the risk for glaucoma progression and visual deterioration.^[3,192]

Retrospective analyses of US claims data suggest that patients receiving latanoprost are significantly less likely to discontinue their medication than those receiving β -blockers (including timolol), carbonic anhydrase inhibitors or brimonidine (section 6).

8.2 Angle-Closure Glaucoma

Angle-closure glaucoma represents fewer than 10% of all diagnosed cases of glaucoma in the US,^[4] but is more common in Asian^[193-196] and Eskimo^[197] populations and is estimated to account for about 50% of glaucoma cases worldwide.^[2] This type of glaucoma is 5 to 10 times more prevalent than open-angle glaucoma in Asian populations.^[193,194]

Angle-closure glaucoma is essentially an anatomical disorder of the anterior segment of the eye in which some form of pupillary block usually restricts the normal flow of aqueous humour through the pupil from the posterior to the anterior chamber increasing IOP in the posterior chamber and causing the iris to obstruct the trabecular meshwork.^[4]

Primary angle-closure glaucoma is further classified as suspect, subacute (incomplete angle closure that resolves spontaneously), acute (rapid and sudden block of aqueous outflow by the iris) and chronic (permanent closure of parts of the anterior chamber angle by peripheral anterior synechia).^[4]

Many patients (particularly those of Asian descent)^[198] with chronic angle-closure glaucoma continue to show elevated IOP despite primary treatment with laser peripheral iridectomy and require additional topical or oral antiglaucoma treatment.^[4] Medical treatment in these patients is generally similar to those used in open-angle glaucoma, and β -blockers (e.g. timolol) are typical first-line agents.

Results of recent clinical studies suggest that latanoprost may also have a role in patients with chronic disease. Indeed, in a large double-blind, randomised study,^[134] latanoprost was more effective than timolol in reducing IOP in these patients. Although these results have not yet been published in full, they are supported by the findings from a smaller, 2-week pilot study in a similar group of patients receiving timolol (section 4.2).^[133] The degree of IOP-lowering with latanoprost in these patients was similar to that in patients with open-angle glaucoma or ocular hypertension (see section 4.1).

In patients where iridectomy is not achievable, or if the peripheral iridectomy site repeatedly closes after laser treatment, surgical iridectomy is indicated. However, if laser peripheral iridectomy is patent, although small in size, iridectomy will have no additional benefit in the control of IOP. The results of one small ($n = 26$) nonblind study suggest that latanoprost as adjunctive therapy may be useful in helping control IOP in iridectomised eyes. Adjunctive latanoprost induced a rapid reduction in IOP, and levels continued to decrease in the small number

of patients who received the drug for up to 1 year (section 4.2).

These results suggest that latanoprost may help avoid the need for further invasive surgical procedures; however, more investigation is necessary in this setting and in patients with angle-closure glaucoma as available data are limited at present. In small trials ($n \leq 36$), latanoprost has shown similar efficacy to timolol in patients with normal-tension and steroid-induced glaucoma (section 4.3). These data also require confirming in larger patient populations

8.3 Tolerability

Most patients with glaucoma require long-term medical treatment to control IOP, so tolerability considerations are important when selecting an agent. Systemic adverse events are a major problem with orally administered carbonic anhydrase inhibitors, and the use of these agents is now limited.^[199] Topically applied drugs clearly produce fewer systemic effects than oral agents; however, these drugs can still enter the systemic circulation through the nasolacrimal drainage system.^[11] Topical β -blockers (particularly nonselective β -blockers such as timolol) cause respiratory and cardiovascular effects that may be particularly problematic in the elderly population who comprise the largest group with glaucoma and who are likely to have a higher incidence of cardiopulmonary disease than the general population. The elderly are also more prone to the other well-established adverse events of non-selective β -blockers.^[189,200] Systemic adverse events are not limited to β -blockers: miotics (e.g. pilocarpine) and α -agonists (e.g. brimonidine) can also cause potentially serious cardiovascular and/or other systemic events.^[199,200]

Adverse events associated with latanoprost are primarily ocular in nature and are generally mild and reversible upon discontinuation of treatment (section 5). Treatment with latanoprost may cause mild conjunctival hyperaemia, eyelash changes and possibly irreversible iridial darkening. Latanoprost should be used with caution in patients with a history of herpes infection. Anecdotal evidence has

suggested development of potentially serious cystoid macular oedema following latanoprost treatment; however, this appears to only occur in patients with independent risk factors for cystoid macular oedema at the time of treatment, such as posterior lens capsule rupture or macular traction. Controlled studies are required to establish whether a causal relationship exists.

Long-term follow-up studies showed that latanoprost is generally well tolerated in patients receiving treatment for up to 2 years (section 5); the tolerability of latanoprost in patients receiving the drug for >2 years has not been established.

A similar incidence of adverse events has been observed between latanoprost and bimatoprost or unoprostone, significantly more conjunctive hyperaemia and increased eyelash growth was reported in bimatoprost than latanoprost recipients whereas headache was more frequently seen in latanoprost than bimatoprost recipients. Latanoprost has shown a similar incidence of total adverse events to both dorzolamide and brimonidine, although systemic effects were more pronounced with dorzolamide.

8.4 Conclusions

Latanoprost 0.005% as a single daily drop has shown good IOP-lowering efficacy in patients with open-angle glaucoma or ocular hypertension. In these patient, latanoprost generally shows superior IOP-lowering efficacy to timolol and does not produce the cardiopulmonary adverse events associated with β -blockers. Latanoprost was also significantly more effective than dorzolamide, brimonidine and unoprostone and generally as effective as bimatoprost and travoprost. The IOP-lowering efficacy of latanoprost was sustained for up to 2 years of treatment. Thus, latanoprost is a valuable addition to the first-line treatment options for patients with open-angle glaucoma or ocular hypertension. In addition, adjunctive treatment with latanoprost in patients who are refractory to β -blocker therapy is a viable, second-line treatment option. Although preliminary findings are promising, wider clinical experience is required to define the place of latanoprost in the

treatment of angle-closure, normal-tension, steroid-induced and pigmentary glaucoma.

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Correspondence: *Tim Ibbotson*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz