Travoprost in the management of open-angle glaucoma and ocular hypertension

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Abstract: Travoprost is a member of the prostaglandin analogue class of intraocular pressure (IOP)-lowering drugs used to treat ocular hypertension and glaucoma. Like other prostaglandin analogues, travoprost lowers IOP by enhancing the egress of aqueous humor through both the uveoscleral and trabecular outflow channels. This review summarizes the published data regarding the safety and efficacy of travoprost. Travoprost provides statistically significant and clinically relevant reductions in mean IOP, of the order of 6.5–9.0 mmHg in most studies. In addition, travoprost provides consistent diurnal IOP control, with statistically significant IOP reductions persisting up to 84 hours post-dose. Travoprost has a highly favorable safety profile; most adverse events are cosmetic in nature (such as iris hyperpigmentation and eyelash growth), although more serious adverse events (such as iritis and macular edema) have been associated with travoprost and the other prostaglandin drugs. In some markets, travoprost is available in a fixed combination with timolol; clinical studies have demonstrated that the fixed combination – dosed once daily – lowers IOP by 7–11.5 mmHg. In conclusion, travoprost provides safe and effective reduction of IOP, with convenient once-daily dosing, supporting its role as primary monotherapy.

Keywords: travoprost, prostaglandin analogue, glaucoma, ocular hypertension, treatment

Management issues in open-angle glaucoma and ocular hypertension

Open-angle glaucoma is an optic neuropathy characterized by progressive loss of retinal ganglion cells and their axons, resulting in progressive loss of the peripheral visual field. Axonal loss is manifested as progressive thinning of the optic nerve head's neuroretinal rim, producing the characteristic cupping of the nerve. If untreated or inadequately treated, glaucoma can lead to blindness.

The prevalence of open-angle glaucoma has recently been estimated at 1.9% in Americans over age 40 (Friedman et al 2004). This prevalence equates to approximately 2.2 million affected individuals in the US in 2004, with an anticipated increase to 3.3 million by the year 2020 (Friedman et al 2004). Worldwide, there will be an estimated 60.5 million people with glaucoma by 2010 and 79.6 million by 2020 (Quigley and Broman 2006). Nearly half of all worldwide glaucoma will occur in Asians (47%), and open-angle glaucoma will account for 74% of all glaucoma by 2020; by 2010, 4.5 million people worldwide will suffer bilateral blindness from open-angle glaucoma; this number will increase to 5.9 million by 2020 (Quigley and Broman 2006).

The pathogenesis of open-angle glaucoma is incompletely understood. Numerous risk factors have been identified. These include intraocular pressure, hispanic or black race, older age, positive family history of glaucoma, thinner central corneal thickness, and possibly myopia and diabetes mellitus. Lacking a clearly elucidated mechanism of disease to target therapeutically, treatment for glaucoma is aimed at risk factor

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modification. Of the risk factors listed above, intraocular pressure (IOP) is the only modifiable risk factor. Reduction of IOP is the only glaucoma therapy proven to be effective. IOP reduction has been shown to delay or prevent the development of glaucoma in eyes with ocular hypertension (Kass et al 2002) and to prevent progression of glaucoma in eyes with (Heijl et al 2002) and without (Collaborative Normal Tension Glaucoma Study Group 1998a, b) elevated IOP.

IOP reduction can be achieved by topical and systemic medications, by various laser therapies, and by a number of incisional surgical techniques. Myriad medications in numerous drug classes are commonly used to achieve IOP reduction. Since first introduced a decade ago, prostaglandins have rapidly become the preferred drug class for glaucoma management. The rapid rise in popularity of the prostaglandin analogues is largely due to the unrivalled efficacy and safety of the drugs in this class, which include travoprost, latanoprost, and bimatoprost.

The purpose of this review is to summarize the clinical data supporting the role of travoprost in the management of ocular hypertension and open-angle glaucoma.

Mechanism of action and pharmacokinetics

Intraocular pressure is determined by the balance between aqueous production and outflow. The majority of aqueous outflow is through the trabecular meshwork, with the remainder egressing through the uveoscleral outflow pathway in normal human eyes. Travoprost appears to lower IOP by facilitating aqueous outflow through both the uveoscleral outflow pathway and the trabecular outflow pathway (Toris et al 2005, 2007).

Mechanism of action

Travoprost, like the other prostaglandin analogues latanoprost and bimatoprost, is a synthetic analogue of prostaglandin $F_{2\alpha}$. Prostaglandins are a family of molecules found ubiquitously throughout most tissues and organs. They are synthesized enzymatically from fatty acids, and all contain 20 carbon atoms, including 5 in a ring formation. Their functions are diverse, and include roles in muscle constriction, inflammation, and platelet aggregation. These various functions are mediated by binding of specific prostaglandins to one or more of numerous prostaglandin receptors. The prostaglandin receptors are transmembrane, G-protein-coupled receptors.

The travoprost molecule is an ester pro-drug that is hydrolyzed by corneal esterases into its active free-acid form. The IOP-lowering efficacy of all three prostaglandin analogues is dependent upon interaction with the prostaglandin FP receptor, as evidenced by the lack of IOP reduction seen with these drugs in eyes of FP receptor-deficient mice (Crowston et al 2004, 2005; Ota et al 2005). Once hydrolyzed in the eye, travoprost acid then binds to prostaglandin FP receptors in both the ciliary muscle (Sharif et al 2002) and the trabecular meshwork (Sharif et al 2003b). In cultured cells from both ciliary muscle and trabecular meshwork in human, rat, and mouse models, travoprost acid exhibits higher binding affinity and higher potency at the FP receptor, and also demonstrates higher selectivity for the FP receptor than for other prostaglandin receptors, than either latanoprost or bimatoprost (Kelly et al 2003; Sharif et al 2002, 2003a, b, c).

FP-receptor binding by prostaglandin $F_{2\alpha}$ and its analogues results in numerous physiologic responses within ciliary muscle cells. These include phosphoinositide turnover, intracellular Ca^{2+} mobilization, and mitogen-activated protein (MAP) kinase activation (Sharif et al 2003c). In addition, FP receptor activation indirectly stimulates formation of cAMP via activation of the coupled G-protein by stimulating the synthesis of PGE_2 (Yousufzai et al 1996; Zhan et al 1998). This in turn leads to increased cellular levels of c-Fos and c-Jun within the nuclei of ciliary smooth muscle cells (Lindsey et al 1994). These two proteins can heterodimerize, forming a complex that binds to the promoter regions of some genes, thus promoting their transcription (Karin et al 1997). The results of these FP receptor-mediated intracellular signals include increased production of several matrix metalloproteinases (MMPs), specifically MMP-1, -2, -3 and -9, in cultured human ciliary smooth muscle cells (Lindsey et al 1997). MMPs are a family of enzymes that are capable of degrading all extracellular matrix components, including collagen. In monkey eyes, topical exposure to prostaglandin $F_{2\alpha}$ reduces collagen types I, II, and IV within the ciliary muscle (Sagara et al 1999). Remodeling of the extracellular matrix of the ciliary body is hypothesized to lower IOP by creating or increasing spaces between the ciliary muscle fiber bundles, thus increasing outflow through the uveoscleral pathway (Schachtschabel et al 2000).

Pharmacokinetics

The esterase-driven hydrolysis of travoprost to its free acid is rapid both in tissue and plasma. In rabbits, following a single topical dose of radiolabeled travoprost 0.004%, the drug distributes throughout all tissues and compartments of the eye, with higher concentrations in the cornea and lower concentrations in posterior segment tissues such as retina and choroid. Plasma levels are also detectable, and decline

in parallel with ocular tissue levels, with half-lives in these tissues of less than 2 hours. Topical ophthalmic application in humans results in systemic absorption with measurable plasma concentrations of both travoprost and travoprost acid (McCue et al 2002). Following one week of once daily dosing of travoprost 0.004%, peak plasma concentrations of travoprost acid up to 25 pg/mL were measured within 30 minutes after dosing. Travoprost acid is rapidly cleared from plasma, with no measurable free acid in samples collected one hour after dosing; because of this short half-life, there is no evidence of accumulation of travoprost acid with once-daily dosing. To evaluate the presence of the travoprost pro-drug in plasma, selected samples underwent esterase hydrolysis and re-analysis of travoprost acid levels. Trace levels were identified in some samples, more commonly in subjects treated with travoprost 0.004% versus 0.0015%, suggesting a dose-proportionality relationship. In addition, plasma levels of travoprost acid in subjects with mild, moderate and severe renal or hepatic impairment are not significantly different from levels in normal subjects, indicating that travoprost dosing adjustments are unnecessary in patients with renal or hepatic impairment.

Efficacy results

Travoprost vs timolol

Phase III evaluation of travoprost's safety and efficacy consisted of three large clinical trials (Goldberg et al 2001; Netland et al 2001; Fellman et al 2002).

Goldberg et al (2001) randomized 573 patients with open-angle glaucoma or ocular hypertension to treatment with either travoprost 0.0015% or 0.004% once daily in the evening or timolol maleate 0.5% twice daily. Enrolled subjects had untreated IOP of at least 24 mmHg, with a mean IOP among all subjects of approximately 26 mmHg. After 9 months of treatment, mean IOP averaged across 6 study visits was lower with travoprost 0.004% than with timolol 0.5% at all time points (9 a.m., 11 a.m., and 4 p.m.) ($p < 0.0246$). Mean IOP reductions ranged from 8.0 to 8.9 mmHg with travoprost 0.004% vs 6.3 to 7.9 mmHg with timolol 0.5%.

Netland et al (2001) randomized 801 patients with open-angle glaucoma or ocular hypertension to one of four treatment regimens: travoprost 0.0015% once daily in the evening, travoprost 0.004% once daily in the evening, latanoprost 0.005% once daily in the evening, or timolol 0.5% twice daily. Enrolled subjects had untreated IOP of at least 24 mmHg, with a mean IOP among all subjects of approximately 25–26 mmHg. After 12 months of treatment, mean IOP averaged across 7 study visits was lower with travoprost 0.004% than with timolol 0.5% at all time points (8 a.m., 10 a.m., and 4 p.m.) ($p = 0.0001$ for all). From similar mean baseline IOP levels of approximately 25.6 mmHg, mean IOP across visits and time points ranged from 17.7 to 19.1 mmHg with travoprost 0.004% vs 19.4 to 20.3 mmHg with timolol 0.5%.

Fellman et al (2002) randomized 605 patients with open-angle glaucoma or ocular hypertension to treatment with either travoprost 0.0015% or 0.004% once daily in the evening or timolol maleate 0.5% twice daily. Across all visits over 6 months of treatment, mean IOP reductions ranged from 6.5 to 8.0 mmHg with travoprost 0.004% vs 5.2 to 7.0 mmHg with timolol 0.5%. Of 13 scheduled IOP measurements over 5 visits, IOP reduction with travoprost 0.004% was statistically superior to that seen with timolol 0.5% at 10 of the 13 time points; at the remaining three time points, IOP reduction was still greater with travoprost 0.004% than with timolol 0.5%, but these differences were not statistically significant. Overall, travoprost 0.004% provided 0.9–2.4 mmHg more IOP reduction than timolol over all 13 time points. Patients receiving travoprost 0.004% were more likely to experience an IOP reduction of 25% or more compared to those receiving timolol 0.5% (62.0%–64.6% vs 37.6%–47.9%, respectively); this difference was particularly evident at 4 p.m. (64.6% vs 37.6%, respectively).

Summarizing the Phase III data, travoprost used once daily lowers IOP by 6.5–9.0 mmHg when used as monotherapy. Travoprost is more effective than timolol in lowering IOP.

Travoprost vs other drugs

Several studies have evaluated the relative IOP reduction provided by the three prostaglandin analogues.

Netland et al (2001) included a latanoprost 0.005% arm in their Phase III evaluation of travoprost. Of 801 enrolled subjects with open-angle glaucoma or ocular hypertension, approximately 200 each were randomized to travoprost 0.004% and latanoprost 0.005%. Mean IOP across all visits was comparable between the two drugs at 8 a.m. and 10 a.m, but at 4 p.m., travoprost lowered IOP by a statistically significant 0.8 mmHg more than latanoprost ($p = 0.0191$).

A prospective, cross-sectional, observational study with retrospective data collection compared the IOP-lowering efficacy of travoprost and latanoprost (Denis et al 2006b). In the study, the time since last instillation and the time of IOP measurement were taken into consideration. Altogether, 2052 patients treated with travoprost ($n = 1704$) or latanoprost ($n = 348$) participated in the study. When the interval between the last treatment instillation and IOP measurement

(treatment/IOP interval) was <24 hours (n = 1241), 82% of travoprost-treated patients achieved pre-defined target IOPs compared with 67% for latanoprost patients ($p < 0.0001$). This difference was largest after 4 p.m., when the mean IOP was 16.5 mmHg for travoprost patients and 17.7 mmHg for latanoprost patients ($p = 0.0025$). When the treatment/IOP interval was >24 hours (n = 461), more patients using travoprost achieved the target IOP (78.5% vs 68.3%; $p = 0.0344$), and the mean IOP value was lower in the travoprost group (16.8 vs 17.8 mmHg; $p = 0.0016$).

Two studies compared the IOP-lowering effect of travoprost versus bimatoprost. In the first, a small study by Cantor et al (2004), 26 subjects with primary open-angle glaucoma or ocular hypertension were randomized to treatment with either travoprost 0.004% or bimatoprost 0.03% once daily in the evening. After 6 months of treatment, mean IOP reductions across visits and time points for travoprost ranged from 4.6 to 7.2 mmHg (19%–29%) vs 7.4–8.8 mmHg (34%–36%) for bimatoprost. These differences were not statistically significant ($p > 0.057$), possibly due to a small sample size and low power to detect differences. A larger, follow-up study of similar design was conducted by Cantor et al (2006), and enrolled 157 subjects. After 6 months of treatment, results of the larger study demonstrated mean IOP reductions with travoprost and bimatoprost were 5.7 vs 7.1 mmHg, respectively, at 9 a.m. ($p = 0.014$); 5.2 vs 5.9 mmHg, respectively, at 1 p.m. ($p = 0.213$); and 4.5 vs 5.3 mmHg, respectively, at 4 p.m. ($p = 0.207$). Responder analysis revealed that statistically similar proportions of patients achieved IOP reductions of ≥20% and ≥30%; investigator-determined clinical success (based on drug tolerability and achievement of target IOP) was statistically equivalent in both groups.

Parrish et al (2003) conducted a three-arm study comparing the three prostaglandin drugs head to head among 410 subjects in a 12-week prospective, randomized trial. This group reported no differences in mean IOP reduction between travoprost (8.0 mmHg), latanoprost (8.7 mmHg), and bimatoprost (8.6 mmHg) ($p = 0.128$).

Franks et al (2006) compared the IOP reduction provided by travoprost with IOP reduction provided by the fixed combination latanoprost 0.005%/timolol 0.5%. In this 6-week study, 110 subjects with open-angle glaucoma or ocular hypertension were randomized to receive either travoprost once daily in the evening or latanoprost/timolol once daily in the morning; masking was achieved by use of a placebo in the morning or evening, depending on randomization. There was no statistically significant difference in IOP reduction between the two groups at any time point. Travoprost lowered IOP by 7.0 mmHg at 9 a.m. compared with 6.4 mmHg for latanoprost/timolol; at 5 p.m., IOP reductions for travoprost and latanoprost/timolol were 6.8 and 6.1 mmHg, respectively.

Suzuki et al (2006) evaluated the relative IOP reduction with travoprost compared with the fixed combination dorzolamide 2%/timolol 0.5%. Fifty-six subjects with open-angle glaucoma or ocular hypertension were randomized to receive either travoprost once daily in the evening or dorzolamide/timolol twice daily; investigators but not subjects were masked to treatment. Mean IOP across all visits and time points was statistically lower with travoprost than with dorzolamide/timolol ($p < 0.01$). At 3 and 6 weeks, mean IOP with travoprost ranged from 7.1 to 7.5 mmHg, compared with 4.5 to 4.8 mmHg with dorzolamide/timolol.

Summarizing the data comparing travoprost with other drugs, similar IOP reductions are seen with travoprost and latanoprost or bimatoprost, the other two members of the prostaglandin class of medications. Travoprost appears to be similar to fixed combinations of timolol with either latanoprost or dorzolamide.

Travoprost and circadian IOP

Circadian IOP variability has emerged as an independent risk factor for the progression of glaucoma (Asrani et al 2000; Nouri-Mahdavi et al 2004). Therefore, the circadian IOP-lowering profiles of medications are a relevant measure of their clinical efficacy. Several studies have evaluated the endurance of travoprost's IOP-lowering effect over periods ranging from 24 to 84 hours post-dose.

Orzalesi et al (2006) conducted a comparison of the 24-hour IOP-lowering profiles of travoprost, latanoprost and bimatoprost. In this crossover study, 44 subjects with primary open-angle glaucoma or ocular hypertension were sequentially treated with each of the three drugs for one month (with a one month washout between each), and underwent 24-hour IOP assessments at pre-treatment baseline and after each month-long treatment session. This group found no statistically significant differences in mean circadian IOP (measured in the sitting position using Goldmann applanation tonometry) between the three drugs. Travoprost produced a mean circadian IOP reduction of 7.1 mmHg, compared with 6.7 mmHg for latanoprost and 7.9 mmHg for bimatoprost ($p = 0.08$). Supine IOP has recently been demonstrated to be generally higher than sitting IOP, and the ability to lower IOP in the supine position (i.e. while asleep at night) is another important aspect of a drug's IOP-lowering profile. The investigators also measured supine IOP using an electronic

tonometer, and found no differences in circadian IOP reduction between the three drugs in the supine position.

Dubiner et al (2004) conducted two studies evaluating the post-dose duration of IOP reduction produced by travoprost. In the first, a small, uncontrolled and open-label pilot study, 21 patients with open-angle glaucoma received travoprost once daily in the evening for 2 weeks. After the final dose on the evening of the 14th day, IOP was assessed every four hours for 36 hours, then again at 60 and 84 hours post-dose. Peak IOP reductions from baseline were in the range of 10.2–11.2 mmHg, and IOP remained statistically below baseline levels throughout the entire 84 hours after the last dose ($p < 0.001$). Mean IOP reduction at 60 and 84 hours post-dose were 7.2 and 6.6 mmHg, respectively. In a follow-up study, 35 patients with open-angle glaucoma were prospectively randomized to receive either travoprost or latanoprost once daily for two weeks in double-masked fashion; 34 patients completed the study. IOP was assessed every 4 hours after the last dose out to 44 hours post-dose. Both travoprost and latanoprost lowered IOP significantly from untreated baseline at all time points ($p \leq 0.001$). Latanoprost provided statistically lower IOP than travoprost (by 2.5 mmHg) 4 hours after the last dose ($p = 0.04$) and travoprost provided statistically lower IOP than latanoprost (by 3.3 mmHg) 24 hours after the last dose ($p = 0.006$). Travoprost also provided lower IOP than latanoprost (by 2.5 mmHg) at the 8PM IOP assessment immediately before the last dose ($p = 0.041$).

Garcia-Feijoo et al (2006) compared the duration of action of travoprost and latanoprost in 62 patients with primary open-angle glaucoma or ocular hypertension. In this prospective, randomized, double-masked trial, patients received once-daily treatment at 8 p.m. for 14 days, and then underwent sitting and supine IOP assessments (using Perkins tonometry) every 4 hours out to 48 hours post-dose. In the sitting position, travoprost produced lower mean IOPs than latanoprost in both the first and second 24-hour periods after the last dose, but these differences did not reach the level of statistical significance. In the supine position, IOP was lower in the travoprost group at every IOP measurement during the 48 hours after the last dose; these differences reached statistical significance at time points 12, 16, 20, 24, 36, 40, and 48 hours after the last dose. Mean IOPs from the periods 0–24, 24–48, and 0–48 hours post-dose were lower for travoprost than for latanoprost in the supine position ($p < 0.05$).

Sit et al (2006) conducted a prospective, open-label study of the duration of travoprost's IOP-lowering effect in 20 subjects with open-angle glaucoma or ocular hypertension. After a baseline, untreated, 24-hour circadian IOP curve was obtained, subjects used travoprost once daily in the evening for at least 4 weeks before undergoing a second 24-hour IOP curve on treatment. One to 8 weeks later, subjects discontinued travoprost and presented for a third 24-hour IOP curve during hours 41–63 following the last dose of travoprost (off treatment). Daytime mean IOP values (between 7 a.m. and 11 p.m.) off treatment remained statistically lower than baseline but statistically higher than on-treatment daytime IOP measurements. Conversely, night-time mean IOP values (between 11 p.m. and 7 a.m.) remained statistically lower than baseline nighttime mean IOP values both on and off treatment, and the on- and off-treatment night-time mean IOP values were identical to one another. This suggests that travoprost's prolonged duration of action is more pronounced at night than during the day.

Summarizing the circadian data, travoprost's duration of action exceeds its 24-hour dosing period. Statistically significant and clinically relevant reductions from baseline are seen up to 63 hours after the last dose of travoprost. Compared with latanoprost, travoprost appears to provide better IOP control at the end of each dosing period. The product is labeled for dosing once daily in the evening.

The fixed combination travoprost/timolol

Fixed combinations of all three prostaglandin analogues – travoprost, latanoprost, and bimatoprost – and timolol have been developed by their respective manufacturers.

The fixed combination travoprost 0.004%/timolol 0.5% has been studied by several investigators. Barnebey et al (2005) enrolled 263 patients with open-angle glaucoma or ocular hypertension into a randomized, multicenter, double-masked trial comparing the fixed combination dosed once daily in the morning with monotherapy with either travoprost 0.004% once daily in the evening or timolol 0.5% twice daily. After 3 months, the fixed combination lowered IOP by 1.9–3.3 mmHg more than timolol monotherapy ($p \leq 0.003$), and by 0.9–2.4 mmHg more than travoprost monotherapy ($p < 0.05$). The fixed combination lowered IOP statistically more than travoprost monotherapy at 7 of 9 IOP assessments during the study. IOP reductions from baseline were in the range of 8.8–11.5 mmHg for the fixed combination, 7.7–9.3 for travoprost, and 6.7–8.7 for timolol across visits and time points.

Schuman et al (2005) compared the fixed combination once daily in the morning to concomitant therapy with travoprost once daily in the evening and timolol twice daily. A third arm received only timolol twice daily. In this pro-

spective, randomized, double-masked, multicenter trial, 403 subjects with open-angle glaucoma or ocular hypertension were enrolled. After 3 months, the fixed combination lowered IOP more from baseline than timolol monotherapy at every visit and time point. In contrast, the concomitant dosing of the separate components produced statistically significantly more IOP reduction from baseline at 2 of 9 time points, with equivalent reductions at the remaining 7 time points. IOP reductions from baseline were in the range of 6.8–8.6 mmHg for the fixed combination, 7.3–8.4 mmHg for travoprost and timolol concomitant therapy, and 4.6–7.0 mmHg for timolol across visits and time points.

Hughes et al (2005) also compared the travoprost/timolol fixed combination with concomitant use of travoprost and timolol. In this prospective, randomized, multicenter, double-masked trial, 316 subjects with open-angle glaucoma or ocular hypertension were assigned to treatment either with the fixed combination dosed once daily in the morning, or with the concomitant administration of travoprost once daily in the evening and timolol once daily in the morning. After 3 months, the upper 95.1% confidence limit for the difference in mean IOP between the two treatment groups was within ±1.5 mmHg at 7 of 9 time points, supporting non-inferiority of the fixed combination compared with concomitant dosing at most time points. The two time points that fell outside this non-inferiority range were both at 10 a.m. on separate visits. IOP reductions from baseline were in the range of 7.4–9.4 mmHg for the fixed combination and 8.4–9.4 mmHg for travoprost and timolol concomitant therapy.

In both of the concomitant vs fixed combination studies, concomitant therapy was more effective at several time points than the combination. This may be attributable to differences in dosing regimens, in which the prostaglandin is given in the morning in the fixed combination group and in the evening in the concomitant group. Prostaglandins are recommended for evening rather than morning dosing. This is partly in an effort to reduce the clinical significance of the transient conjunctival hyperemia that occasionally follows topical dosing (see Safety and Tolerability below). In contrast, beta-blockers generally lower IOP more effectively with morning rather than evening dosing (Ong et al 2005) as a consequence of the natural reduction of aqueous production at night (Reiss et al 1984) which essentially requires morning dosing for the fixed combination.

Denis et al (2006a) have evaluated the efficacy of the travoprost/timolol fixed combination when dosed in the morning versus evening. In this prospective, randomized, double-masked trial, 92 subjects with open-angle glaucoma or ocular hypertension received the fixed combination either in the morning or the evening for 6 weeks. IOP reductions were similar in both groups, ranging from 16.5 to 16.7 mmHg in the morning group and 16.1 to 17.2 mmHg in the evening group. IOP reductions from baseline were statistically significant and clinically relevant in both groups, with mean IOP reductions of 8–10 mmHg (32%–38%).

The travoprost/timolol fixed combination has been approved in the EU, Canada, and Australia, but has not been approved by the US Food and Drug Administration to date.

Safety results

The side-effects of the prostaglandin analogues have recently been reviewed elsewhere (Hollo 2007). The adverse effects associated with travoprost have been identified both in large clinical trials and in small series and case reports. Without exception, the adverse effects seen with travoprost therapy are identical in nature to those associated with all other members of the prostaglandin analogue class of IOP-lowering medications. Although most of these adverse effects do not pose a threat to vision or health, a few potential safety issues have been identified. Among the former are conjunctival hyperemia, iris hyperpigmentation, eyelash changes, and periocular hyperpigmentation; and among the latter are the possibility of iritis and/or macular edema. Each of these potential adverse effects has been reported with at least one of the prostaglandins analogues. In the following section, travoprost's relationship with each of these events will be discussed.

Conjunctival hyperemia

The incidence of hyperemia ranged from 32.5% to 49.5% for travoprost 0.004% vs 7% to 14% for timolol maleate 0.5%. In most cases, the hyperemia was trace to mild in severity, and discontinuation from the study was uncommonly (< 5%) due to hyperemia (Goldberg et al 2001; Netland et al 2001; Fellman et al 2002). In at least one study, the hyperemia improved over time with continued dosing (Goldberg et al 2001).

The relative incidence of hyperemia between prostaglandins has also been evaluated. Netland et al (2001) reported a 27.6% incidence of hyperemia in eyes receiving latanoprost versus 49.5% in travoprost-treated eyes. Cantor et al (2006) reported hyperemia in 21.1% of eyes receiving bimatoprost vs 14.8% in travoprost-treated eyes. In the three-way head-to-head trial reported by Parrish et al (2003), the incidences of hyperemia for travoprost, latanoprost, and bimatoprost were 58%, 68.6%, and 47.1%, respectively. Also, in a trial

by Lewis et al (2007), comparing travoprost with BAK with travoprost without BAK, the incidences of subject-reported hyperemia were 9.0% and 6.1%, respectively.

The reported rates of conjunctival hyperemia vary significantly even for individual drugs. This likely is a result of non-standardized methods for evaluating hyperemia. Methodologies for evaluating hyperemia in these studies ranged from patient complaint to subjective investigator grading of hyperemia based on tiered scoring systems to photographic evaluation using internal color strips in the images to account for differences in photographic techniques between individuals. To date, there has been no evidence supporting that conjunctival hyperemia poses a threat to vision or health, and that this adverse effect is simply a cosmetic issue.

Iris hyperpigmentation

Darkening of the iris is a well-established consequence of therapy with all three of the prostaglandin analogues. The incidence varies from study to study based on differences in methodology, as with conjunctival hyperemia. In the three Phase III registry trials, the incidence of iris hyperpigmentation in eyes treated with travoprost 0.004% ranged from 1.0–3.6% versus 0% of timolol-treated eyes (Goldberg et al 2001; Netland et al 2001; Fellman et al 2002).

In the study by Netland et al (2001), 5.2% of eyes receiving latanoprost, vs 3.1% of eyes receiving travoprost, developed iris hyperpigmentation. Cantor et al (2006) reported a single case of iris hyperpigmentation in their 157-subject comparison of travoprost vs bimatoprost; it occurred in a bimatoprost-treated eye.

The incidence of iris hyperpigmentation in these relatively short (6–12 months) studies is low. The long-term incidence of iris hyperpigmentation was evaluated for latanoprost in a prospective, open-label study, consisting of a three-year initial phase (n = 519) and a 2-year extension (n = 380) (Alm et al 2004). Overall, 33.4% of eyes experienced a change in eye color with up to 5 years of exposure to once-daily latanoprost. Time-course analysis revealed that 74% of eyes experiencing iris hyperpigmentation manifested the change within the first 8 months of treatment, and 94% within the first 24 months, with no additional new cases noted beyond month 36 of treatment.

The risk of experiencing iris hyperpigmentation appears to depend on baseline eye color. Green and mixed hazel eyes are at greatest risk, while blue and grey eyes appear to be infrequently affected. In the 5-year study of latanoprost conducted by Alm et al (2004), no subjects with brown or blue/grey eyes were affected, while more than 75% of green-brown or yellow-brown eyes were affected.

This clinical observation regarding eye color and risk of iris hyperpigmentation is consistent with histopathological studies demonstrating that topical prostaglandin therapy induces an increase in melanin production within existing melanocytes, with no evidence of melanocyte proliferation (Pfeiffer et al 2001, 2003; Cracknell et al 2003; Albert et al 2004; Arranz-Marquez et al 2004). Of these, the most robust evaluation was by Albert et al (2004), who undertook a large, masked histopathological evaluation of 449 latanoprost-exposed iris specimens compared with 142 control specimens. There was no evidence of malignancy or pre-malignant changes in any specimen. Latanoprost-treated eyes had more iris freckles than controls (35% vs 20.6%, $p = 0.001$); the authors stated that in their opinion, they "do not believe that the increase in iris freckles has malignant potential or can lead to any adverse clinical effects on the eye". They postulated that these freckles were focal manifestations of iris hyperpigmentation. Using immunohistochemical staining, they reported "no significant difference in mean melanocyte counts…between the latanoprost-treated and control groups". They concluded that iris hyperpigmentation in latanoprost-treated eyes was "due to an increased amount of melanin within the iris stromal melanocytes".

As with conjunctival hyperemia, iris hyperpigmentation associated with travoprost therapy appears to be a cosmetic issue that poses no known threat to vision or health. The incidence appears to be low – below 5% – in studies involving up to one year of daily exposure to travoprost 0.004%. The potential for eye color changes should be discussed with patients prior to the initiation of treatment, but in practice, patients rarely express concern regarding the possibility of this adverse event, and rarely self-report changes in eye color despite long-term therapy with these drugs. Greater caution should be employed in cases where monocular treatment is required, as unilateral iris hyperpigmentation may have a greater cosmetic impact than bilateral. This issue is easily overlooked after successful unilateral filtering surgery, in which preoperative bilateral prostaglandin therapy becomes unilateral therapy upon discontinuation of treatment in the operated eye.

Eyelash changes

Travoprost and the other prostaglandin analogues can induce specific changes in the appearance of the eyelashes, including lengthening, thickening, and darkening of the lashes, as well as an increase in the number of lashes. These changes are

common in eyes treated with all three drugs (Goldberg et al 2001; Netland et al 2001; Fellman et al 2002).

Based on these trials, a majority of patients treated with travoprost for at least 6 months can anticipate some degree of lash changes. These changes appear to be cosmetic in nature and do not pose a threat to vision or health. Based on the similar incidences of lash changes for travoprost at 6 (Fellman et al 2002), 9 (Goldberg et al 2001), and 12 months (Netland et al 2001) it appears that lash changes generally manifest within the first 6 months of therapy.

Periocular hyperpigmentation

Eyelid hyperpigmentation has been reported in association with the use of latanoprost (Kook and Lee 2000; Wand et al 2001a, b; Herndon et al 2003) and bimatoprost (Herndon et al 2003; Herane and Urbina 2004; Galloway et al 2005) and was also observed in regulatory trials with travoprost (Golberg et al 2001; Netland et al 2001; Fellman et al 2002). Eyelid hyperpigmentation appears to be a rare side-effect of the prostaglandin class of IOP-lowering medications. Based on limited histopathological data from Kapur et al (2005), the mechanism of eyelid hyperpigmentation appears similar to that of iris hyperpigmentation, characterized by increased melanogenesis and not melanocyte proliferation; the investigators concluded that prostaglandin-induced eyelid hyperpigmentation "occurs from increased melanogenesis…with the absence of melanocyte proliferation and melanocyte atypia". Unlike iris hyperpigmentation, hyperpigmentation of the eyelid appears to improve (Kook and Lee 2000; Wand et al 2001b; Herndon et al 2003; Herane and Urbina 2004; Galloway et al 2005) – and in some cases resolve completely (Galloway et al 2005) – upon discontinuation of the drug. All existing data to date support that these changes are solely cosmetic in nature, and have not posed a health risk in any form.

Iritis

Iritis is infrequently reported in association with use of the prostaglandin drugs, and the causal relationship between use of these drugs and the occurrence of intraocular inflammation has been debated. The association between prostaglandins and iritis was reported by several groups, including Fechtner et al (1998), who reported 5 eyes of 4 patients who developed iritis after beginning therapy with latanoprost, recovered after discontinuation of the drug, and experienced recurrent iritis upon rechallenge. The incidence of latanoprost-induced iritis was determined retrospectively in a cohort of 94 patients by Warwar et al (1998), who reported iritis in 8 eyes of 6 patients (4.9% of eyes, 6.4% of patients) treated with latanoprost. Three of the 6 patients were rechallenged, and 2 manifested recurrent iritis. Bimatoprost has also been reported to cause iritis (Packer et al 2003; Parentin 2003). Travoprost can also induce iritis, as reported by Kumarasamy and Desai (2004) in which iritis appeared after initiating therapy with travoprost and resolved with discontinuation.

To determine the relative effects of the three prostaglandin analogues on the integrity of the blood-aqueous barrier, Cellini et al (2004) evaluated anterior chamber and cell and flare values in 60 glaucoma patients randomly assigned to treatment with travoprost, latanoprost, or bimatoprost for six months. The researchers employed a flare meter to quantify both cell and flare at baseline and after 3 and 6 months of therapy. All 3 drugs were associated with statistically significant increases in cell and flare from baseline at 3 and 6 months, with little diminution of cell or flare from 3 to 6 months. Latanoprost induced significantly more cell and flare than either travoprost or bimatoprost at 3 and 6 months. Travoprost induced more cell and flare than bimatoprost at 3 months, but by 6 months the levels were statistically equivalent.

In the study by Cellini et al (2004), the phakic status of the eyes of participating subjects was not described. Arcieri et al (2005) recently performed a similar trial in 34 phakic individuals. In a crossover design, subjects received each drug (travoprost, latanoprost, and bimatoprost) for 4 weeks with a 4-week washout between each crossover. In these phakic eyes, there was no increase from baseline in anterior chamber flare with any of the 3 drugs, nor any between-drug differences in flare levels.

Symptomatic iritis appears to be an uncommon adverse event associated with all three prostaglandin analogues. The course is generally mild and the inflammation resolves upon discontinuation of the drug with or without anti-inflammatory therapy. Interestingly, a significant proportion of the eyes in the studies referenced above had either a prior history of iritis or had risk factors (such as prior cataract surgery with or without complications) predisposing to iritis. From these observations, the use of prostaglandin analogues in eyes with a history of iritis, or with risk factors for iritis, should occur with caution. Also, based on the high rates of positive rechallenges, reinitiating therapy after an episode of iritis may not be advisable.

Macular edema

Macular edema was not noted as a side-effect of the prostaglandins in Phase III trials, but as with iritis, post-marketing

reports have suggested a relationship that has been debated. Case reports and small series of macular edema have been reported in association with all 3 prostaglandin analogues (Carrillo and Nicolela 1994; Ayyala et al 1998; Callanan et al 1998; Gaddie and Bennett 1998; Moroi et al 1999; Wand et al 2001a, b; Tokunga et al 2002; Jager and Jonas 2003; Watanabe et al 2003; Del Hierro et al 2004; Altintas et al 2005). Virtually all of these cases included eyes with other risk factors for macular edema, most commonly prior cataract surgery (both complicated and uncomplicated). In cases where post-discontinuation outcomes were reported, macular edema resolved, and visual acuity returned to baseline, upon discontinuation of the prostaglandin with or without anti-inflammatory treatment (Ayyala et al 1998; Moroi et al 1999; Wand et al 2001a; Tokunaga et al 2002; Jager and Jonas 2003; Watanabe et al 2003; Carrillo and Nicolela 2004; Altintas et al 2005).

The incidence of macular edema in eyes treated with latanoprost was reported by Warwar et al (1998). In their cohort of 163 predominantly phakic eyes of 94 patients, 2 eyes of 2 patients developed macular edema (1.2% of eyes, 2.1% of patients). Lima et al (2000) reported an incidence of 2.2% among 185 pseudophakic or aphakic patients treated with latanoprost. Yeh et al (2002) found an incidence of 3.0% in 134 pseudophakic eyes treated with latanoprost after uncomplicated cataract surgery and with no history of or risk factors for macular edema. In contrast, Furuichi et al (2001) reported no increase in macular thickness, as measured by optical coherence tomography, in 68 eyes of 38 glaucoma patients treated with latanoprost who had no history of intraocular surgery or other risk factors for macular edema.

The true cause of macular edema in eyes receiving latanoprost therapy has been extensively evaluated by Miyake et al (1999). In an early study of 145 glaucomatous or ocular hypertensive eyes scheduled for elective cataract surgery, eyes receiving latanoprost for 5 weeks postoperatively developed more angiographic macular edema than eyes receiving placebo, and diclofenac was more effective than fluorometholone in suppressing latanoprost-associated macular edema. On closer inspection, however, the latanoprost vehicle, and particularly the preservative – BAK – was suspected to be the causal factor in inducing macular edema. In a follow-up study, the incidence of macular edema following cataract surgery was equivalent in eyes receiving timolol maleate solution preserved with BAK and in eyes receiving timolol vehicle with BAK, and was significantly lower in eyes receiving timolol vehicle without BAK (Miyake et al 2001). These observations led Miyake et al (2003) to coin the term "pseudophakic preservative maculopathy" in an effort to clarify that macular edema can arise in association with treatment with any BAK-preserved topical medication.

In summary, macular edema can occur as a rare side-effect in eyes treated with travoprost or other prostaglandin analogues. Pseudophakic eyes and eyes with other risk factors for macular edema are most likely to be affected, and phakic eyes without risk factors may not be at risk. The edema resolves, and visual acuity returns, upon cessation of prostaglandin therapy.

Systemic safety

Travoprost, like all members of the prostaglandin class of IOP-lowering medications, is extremely well-tolerated systemically. In Phase III clinical trials with travoprost, no systemic side effects were noted to occur statistically more often in travoprost-treated subjects than in subjects treated with timolol (Goldberg et al 2001; Netland et al 2001; Fellman et al 2002) or latanoprost (Netland et al 2001). In addition, post-marketing surveillance has not revealed any unanticipated systemic adverse events associated with travoprost or other prostaglandin analogues. Travoprost has no appreciable effect on the cardiovascular or pulmonary systems, and does not alter hematology, blood chemistry, or urinalysis laboratory values (Inan et al 2004).

Travoprost is classified as a pregnancy category C drug. Travoprost was teratogenic in rats receiving 250 times the maximum recommended human ocular dose (MRHOD) but not at 75 times the MRHOD, but a higher risk of fetal loss was noted with the latter dose. The package insert advises that "there are no adequate and well-controlled studies in pregnant women," and recommends that the drug be used in pregnant women "only if the potential benefit justifies the potential risk to the fetus" (Alcon Laboratories, Inc, 2006)

Patient-focused considerations

Quality of life

Quality of life (QOL) assessments with glaucoma patients can be accomplished by using one or more of a number of different instruments that are available (Spaeth et al 2006).

However, the impact on QOL of decreased vision as an outcome of uncontrolled IOP and progressing glaucoma disease typically occurs over a long period of time. The consequences of reduced vision are serious but patients are also focused on the things that currently impact their daily life such as how satisfied they are with their treatment regimen.

Patient treatment satisfaction/ acceptability

The Treatment Satisfaction Survey for Intraocular Pressure (TSS-IOP) was developed to identify factors associated with patient satisfaction with glaucoma therapy. The instrument queries patients receiving IOP-lowering therapy on issues pertaining to various aspects of glaucoma management and topical medical therapy, and was recently validated in 250 subjects with glaucoma or ocular hypertension (Atkinson et al 2003; Day et al 2006). In this study, patient satisfaction positively correlated with effectiveness of therapy, lack of side effects, and ease and convenience of use. Of note, travoprost and the other prostaglandin analogues are characterized by each of these satisfaction-promoting characteristics, with unrivaled safety and efficacy, as well as convenient once-daily dosing.

Looking at satisfaction from an economic point of view, Jampel et al (2003, 2005) conducted a pair of studies to determine both patients' and physicians' willingness to pay for specific characteristics of an IOP-lowering medication. Their findings were insightful. One hundred thirteen members of the American Glaucoma Society were presented with a hypothetical IOP-lowering drug costing US$50 per month and asked how much, if at all, they would be willing to pay to improve specific aspects of the drug (Jampel et al 2005). For instance, assuming that the $50 drug caused a mild bad taste in the mouth, 91% of glaucoma specialists were willing to pay an average of $81 (a $31 premium) to avoid the bad aftertaste. In the study, the top attributes worth paying extra to avoid were as follows: 100% of physicians were willing to pay more (mean $92) for a drug that did not cause blurred vision; 99% would pay more (mean $105) to avoid sexual performance side-effects; 98% would pay more (mean $87) to reduce dosing from 3 times daily to once daily; and 97% would pay more (mean $92) to avoid drowsiness. In contrast, the following were the attributes least concerning to physicians: only 48% would pay more (mean $79) to avoid a small risk of iris hyperpigmentation; 60% would pay more (mean $69) for a drug available in generic form; and 88% would pay more (mean $71) for a combination product that reduced a two-bottle regimen to a one-bottle regimen.

The same scenarios were presented to 230 glaucoma patients in 4 distinct practices (Jampel et al 2003), and the differences in their valuations of these drug attributes, compared to physicians, are remarkable. The top 5 attributes patients wished to avoid (with % willing to pay more to avoid that attribute, and the mean amounts they were willing to pay to avoid it) were as follows: blurred vision (85%, $71); drowsiness (83%, $69); bad aftertaste (76%, $66); and stinging/tearing upon instillation (72%, $62). The attributes for which patients were least willing to pay extra to avoid were: availability of a generic (26%, $54); reduction from 3 times daily to twice daily dosing (38%, $56); a combination product eliminating one bottle of medication (43%, $58); reduction from 3 times daily to once daily dosing (59%, $63); and sexual performance side-effects (59%, $68).

The attributes patients want most to avoid – blurred vision, drowsiness, bad aftertaste, and stinging upon instillation – are all uncommon with travoprost and other prostaglandin analogues. Interestingly, there is something

Table 1 Summary of key travoprost monotherapy efficacy data

Study	Comparator	No. of subjects	Summary of findings
Goldberg et al 2001	Timolol	573	Mean IOP lower with travoprost than timolol at all time points ($p \leq 0.0246$)
Netland et al 2001	Timolol	801	Mean IOP lower with travoprost than timolol across all time points ($p = 0.0001$)
Netland et al 2001	Latanoprost	801	Mean IOP similar at 8 a.m. and 10 a.m. but lower at 4 p.m. with travoprost than latanoprost ($p = 0.0191$)
Fellman et al 2002	Timolol	605	Mean IOP lower with travoprost than timolol at 10 of 13 time points ($p \leq 0.03$)
Denis et al 2006a, b	Latanoprost	2052	More eyes reached target IOP with travoprost than latanoprost ($p \leq 0.0344$)
Cantor et al 2004, 2006	Bimatoprost	157	Mean IOP similar at 1 p.m. and 4 p.m. but lower with bimatoprost than travoprost at 9 a.m. ($p = 0.014$)
Parrish et al 2003	Latanoprost	410	Mean IOP similar with both drugs ($p > 0.05$)
Parrish et al 2003	Bimatoprost	410	Mean IOP similar with both drugs ($p > 0.05$)
Franks et al 2006	Latanoprost/Timolol	110	Mean IOP similar with both drugs ($p > 0.05$)
Suzuki et al 2006	Dorzolamide/Timolol	56	Mean IOP lower with travoprost than dorzolamide/timolol ($p < 0.01$)

Abbreviations: IOP, intraocular pressure

Table 2 Summary of key travoprost safety data

Safety event	Incidence in eyes treated with travoprost	References
Conjunctival hyperemia	32.5%–49.5%	Goldberg et al 2001; Netland et al 2001; Fellman et al 2002
Iris hyperpigmentation	1.0%–3.6%	Goldberg et al 2001; Netland et al 2001; Fellman et al 2002
Eyelash changes	51%–76.2%	Goldberg et al 2001; Netland et al 2001, Fellman et al 2002
Periocular hyperpigmentation	Rare	Goldberg et al 2001; Netland et al 2001; Fellman et al 2002
Iritis	Rare	Kumarasamy and Desai 2004
Macular edema	Rare	Del Hierro et al 2004

of a disconnect between what physicians and patients value in a medication. Physicians put great value on once-daily dosing and avoidance of sexual side-effects, while these are of considerably less relative concern to patients. Conversely, while physicians are willing to tolerate mild stinging and tearing upon instillation, this is highly bothersome to patients. These insights may be of value to physicians when developing treatment plans for their patients.

Therapeutic compliance

Compliance assessment in glaucoma has evolved in recent years. New terms such as adherence and persistency have been introduced. Persistency is an indirect measure of compliance derived from prescription refill rates. The information is obtained not from the patient or physician, but from managed care databases in which members have a single central source for prescription drugs. Persistency is a measure of the time from initial prescription until the patient stops refilling the medication. As a result, low persistency can arise either from patient noncompliance or from physicians making changes in therapy, and is a useful parameter by which to gauge the length of time a drug is used or useful before either the patient or physician discontinues its use.

Persistency with glaucoma medications has been measured in several studies. Wilensky et al (2006) studied persistency in over 2000 glaucoma patients on prostaglandin therapy. Of patients who persisted for at least 3 months upon beginning treatment, the percentages of patients still on the same treatment 12 months after starting therapy were 70.6% for travoprost, 69.4% for latanoprost, and 68.1% for bimatoprost. While these data suggest comparable persistency among the various prostaglandin analogues, a second study did not confirm this.

In a different twist on persistency with initial prostaglandin therapy, patients in the Medco Health database who initiated prostaglandin therapy were followed if they were still taking their initial prostaglandin at 12 months. Overall, 39% of travoprost patients needed to add a second glaucoma medication within that 12-month time period compared with 39% of bimatoprost patients and 51% of latanoprost patients ($p < 0.0001$). This relative difference was consistent when looking at the subsets of patients' naïve to glaucoma therapy and those using a non-prostaglandin drug before they started using prostaglandin therapy (Covert and Robin 2006).

Recently, Alcon Laboratories (manufacturers of travoprost) have developed and introduced an electronic dosing aid designed to remind patients to take their drops, to facilitate instillation of drops, and to record each administered dose for compliance monitoring. The device is a small housing into which a commercial bottle of travoprost is placed. The device is programmable to remind patients to dose at their preferred time, with flashing lights or an audible beeping alarm or both. The device has a lever that is calibrated to dispense a single drop of travoprost when pressed; this lever may be helpful to patients with arthritis or tremors who have difficulty squeezing the small bottle with appropriate force to dispense a single drop. Additionally, the device electronically records the date and time of each activation of the lever. When returned to the physician's office, the device is placed in a docking cradle attached to a computer, and the provided software generates a dosing schedule.

The dosing aid was recently evaluated in a study by Boden and colleagues (2006). Ten volunteers used the device to instill artificial tears over 15 days; each was assigned a schedule designed to mimic compliance rates ranging from 50% to 100% compliance. Participants recorded their dosing schedule in a journal, which was then compared with the electronic device's compliance report. They found that date stamping was 100% accurate, and time stamping was generally accurate to within $\pm$20 minutes. The device failed to record at least one drop in 70% of patients, suggesting that the device may provide an underestimate of true compliance.

Conclusions/place in therapy

Travoprost is an effective IOP-lowering medication, providing 6.5–9.0 mmHg of IOP reduction when used as

monotherapy. Its efficacy is equivalent to other drugs in the prostaglandin class, and at least as effective as combination products pairing timolol with latanoprost or dorzolamide. Travoprost may have added efficacy in black patients and eyes with pseudoexfoliation, and post-marketing studies have demonstrated its efficacy in eyes with chronic angle closure glaucoma, and following cataract surgery, although the product is not specifically indicated for these latter two conditions. Its duration of action is longer than its 24-hour dosing period, with significant IOP reductions from baseline as long as 63 hours after the last dose, but once-daily dosing is recommended. The data suggest that travoprost provides greater IOP control at the end of each dose than does latanoprost. Travoprost's established ocular side-effects are generally cosmetic in nature (conjunctival hyperemia, iris and eyelid hyperpigmentation, eyelash changes), with few reports of iritis and macular edema; side-effects of travoprost are similar to side-effects of other prostaglandin drugs, supporting that these are class effects. Given its excellent safety and efficacy profile, its convenient once-daily dosing, and its widespread global availability, travoprost is commonly used as first-line therapy for glaucoma (although currently only indicated for second-line therapy in the US). Five years of post-marketing surveillance in the United States, where it first gained regulatory approval in 2001, has confirmed the safety and efficacy results of Phase III trials, and supports its role as primary monotherapy.

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