REVIEW ARTICLE

Drug Safety 2002; 25 (8): 583-597
0114-5916/02/0008-0583/$25.00/0

Safety of Unoprostone Isopropyl as Mono- or Adjunctive Therapy in Patients with Primary Open-Angle Glaucoma or Ocular Hypertension

Paulo Augusto de Arruda Mello,[1] *Natalia C. Yannoulis*[2] and *Reza M. Haque*[3]

1 Department of Ophthalmology, Federal University of Sao Paulo-Paulista School of Medicine and Director Residency Training, Sao Paulo, Brazil
2 Novartis Ophthalmics AG, Bülach, Switzerland
3 Novartis Ophthalmics, Inc., Duluth, Georgia, USA

Contents

Abstract . . . 583
1. Description of Unoprostone 0.15% Studies . . . 584
   1.1 Patient Selection . . . 585
   1.2 Safety Variables and Analyses . . . 586
2. Safety of Unoprostone 0.15% as Monotherapy . . . 587
   2.1 Patient Demographics and Baseline Characteristics . . . 587
   2.2 Adverse Events . . . 587
   2.3 Other Examinations . . . 589
3. Safety of Unoprostone 0.15% as Adjunctive Therapy . . . 590
   3.1 Patient Demographics and Baseline Characteristics . . . 590
   3.2 Adverse Events . . . 590
   3.3 Other Examinations . . . 592
4. Safety of Unoprostone 0.15% in Special Populations . . . 592
5. Safety of Unoprostone 0.12% as Monotherapy . . . 592
6. Safety of Unoprostone 0.12% as Adjunctive Therapy . . . 593
7. Discussion . . . 594
8. Conclusions . . . 595

Abstract

This review summarises the safety of unoprostone isopropyl (both at the 0.12 and 0.15% concentrations) instilled twice daily in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OH). For unoprostone 0.15%, combined data from two 12-month comparative monotherapy studies are reported, as well as data from three adjunctive therapy studies and two special population studies. With unoprostone monotherapy, most adverse events were mild or moderate and transient in nature. Less than 7% of unoprostone-treated patients discontinued therapy due to an adverse event. The most common adverse events associated with unoprostone were burning/stinging, burning/stinging directly upon drug instillation, ocular itching, and conjunctival hyperaemia. Un-

oprostone had no clinically notable effects on vital signs, laboratory profiles, or comprehensive ophthalmic examinations. One of 659 unoprostone 0.15%-treated patients had a change in iris colour after 12 months of monotherapy. Except for a higher incidence of burning/stinging and burning/stinging upon instillation, unoprostone was comparable to timolol 0.5% twice daily and betaxolol 0.5% twice daily. No safety concerns were raised with use of unoprostone as adjunctive therapy. Unoprostone had no significant effect on exercise-induced heart rate in healthy subjects or on pulmonary function in patients with mild-to-moderate asthma. The safety profile of unoprostone 0.15% was consistent with published information on the 0.12% formulation. In conclusion, unoprostone has an excellent safety profile in patients with POAG or OH.

In 1994, an ophthalmic solution of unoprostone isopropyl 0.12% (Rescula®,[1] Ueno Fine Chemicals Industry Ltd.) was approved in Japan for use in patients with primary open angle glaucoma (POAG) or ocular hypertension (OH). Japanese studies conducted in support of this approval demonstrated that unoprostone 0.12% significantly reduces intraocular pressure (IOP), enhances ocular blood flow[1-7] and has an excellent safety profile, both as mono- and adjunctive therapy.[8-16] Systemic adverse effects associated with use of unoprostone 0.12% are very rare, and ocular events are generally mild and transient in nature, with burning/stinging being the most common event reported. Since its approval in Japan, unoprostone 0.12% has been used to treat over 500 000 patients in that country.

More recently, Novartis Ophthalmics (formerly CIBA Vision) obtained worldwide licensing rights (except for Japan, Korea, and Taiwan) to develop and market unoprostone as an antiglaucoma agent. Further investigations were conducted, including extending dose ranging studies to include 0.15%,[17] to confirm the safety and efficacy of unoprostone in non-Japanese patients. In 2000, unoprostone isopropyl 0.15% (Rescula®) became the first docosanoid-type drug to gain US approval for the treatment of patients with POAG or OH. It may be used as adjunctive therapy to other medications such as β-blockers[18] or latanoprost[19] or as monotherapy in patients who are intolerant of or insufficiently responsive to other IOP-lowering medications.[20] Alongside the IOP lowering ability of unoprostone, it has been shown to possess positive effects on ocular blood flow, both in *in vitro* and animal models[21,22] as well as healthy human volunteers.[23] Additionally unoprostone displays neuroprotective properties *in vitro* and *in vivo* models.[24-26]

The purpose of this review is to report on the safety and tolerability of unoprostone, both at the 0.12% concentration, and for the newly-approved 0.15% formulation, based on results of US and European regulatory trials, as an anti-glaucoma agent in patients with POAG or OH, both as mono- and adjunctive therapy. Safety data from seven clinical trials conducted as part of the drug development programme for unoprostone 0.15% are summarised. Twelve-month data from two 24-month comparative monotherapy studies (C4, C5) and three adjunctive therapy studies (C11, C14, C15) are summarised, as well as data from two special population studies (C12, C13).[20,27-31] The data reviewed for unoprostone 0.12% were obtained from the literature and are mainly from Japanese regulatory trials.

1. Description of Unoprostone 0.15% Studies

The two monotherapy studies (C4, C5) were very similar in design, with each being a randomised, double-blind, active-controlled, parallel-group, multicentre study. The C4 study was

1 The use of tradenames is for product identification only and does not imply endorsement.

conducted at 30 sites in the US and Canada; C5 was conducted at 27 sites in Europe and Israel. In the C4 study, eligible patients were randomised in a 2 : 1 ratio to instil one drop of unoprostone 0.15% (Rescula®) twice daily or timolol 0.5% (Timoptic®) twice daily into each eligible eye for 24 months. Likewise, in the C5 study, patients were randomised in a 2 : 1 : 1 ratio to instil one drop of unoprostone 0.15% twice daily, timolol 0.5% twice daily, or betaxolol 0.5% (Betoptic®) twice daily for 24 months. In both studies, patients discontinued use of prior ocular hypotensive therapy for a specified period of time (at least 4 weeks for topical β-blockers or topical unoprostone at least 2 weeks for topical α-agonists or epinephrine (adrenaline)-related medication, and at least 3 days for topical pilocarpine or carbonic anhydrase inhibitors), before starting randomised therapy. Prospectively-planned interim analyses were conducted for both studies after each patient completed 12 months of therapy; this review summarises the results of these analyses.

The C11 study was a randomised, double-blind, active-controlled, parallel-group, multicentre (14 sites) study that evaluated unoprostone 0.15% (Rescula®) twice daily, dorzolamide 2.0% (Trusopt®) twice daily, and brimonidine 0.2% (Alphagan®) twice daily as adjunctive therapy to timolol 0.5% (Timoptic®) twice daily. After a 2-week run-in period with timolol monotherapy, patients instilled one drop of double-blind study medication twice daily as adjunctive therapy to timolol for another 12 weeks.

The other two adjunctive therapy studies (C14, C15) were randomised, double-blind, placebo-controlled, parallel-group studies that compared the safety of unoprostone 0.15% versus placebo as adjunctive therapy to brimonidine 0.2% (Alphagan®, C14) or dorzolamide 2.0% (Trusopt®, C15) over a 4-week period. In both studies, patients first instilled one drop of brimonidine 0.2% three times daily (C14) or dorzolamide 2.0% three times daily (C15) for 4 weeks; thereafter, patients instilled one drop of double-blind unoprostone 0.15% twice daily or placebo as adjunctive therapy to brimonidine 0.2% three times daily or dorzolamide 2.0% three times daily for another 4-week period.

The C12 study was a randomised, double-blind, three-treatment, three-period crossover study that evaluated the cardiovascular effects of unoprostone 0.15%, timolol 0.5% (Timoptic®), and placebo in healthy volunteers during exercise. Drugs were administered twice daily for 5 days, with a 9- to 10-day washout between treatments. Fifteen minutes after administration, patients underwent a submaximal 15-minute treadmill test, with a 15-minute recovery. The C13 study was a randomised, double-blind, crossover, placebo-controlled study that evaluated the effect of unoprostone 0.15% on pulmonary function in patients with mild-to-moderate asthma. Patients underwent spirometric testing after receiving a single drop of unoprostone 0.15% or placebo in both eyes. Testing was repeated 3 days later after patients crossed over to alternate therapy.

1.1 Patient Selection

For the sake of brevity, only the main selection criteria for each study are described in this review. Before the studies were initiated, an institutional review board or ethics committee approved the protocol and informed consent form in compliance with US regulations and applicable local regulations. All participants signed an informed consent.

In the monotherapy studies, patients (male or female, any ethnicity) had to be ≥18 years of age and have uni- or bilaterally elevated IOP associated with POAG or OH. After washout of prior therapy, patients had to have an IOP ≥22 and ≤30mm Hg in eligible eyes at one or more timepoints during a baseline 12-hour diurnal IOP evaluation. Patients were excluded if they had a history of topical, ocular prostaglandin-type therapy, required more than one ocular hypotensive medication, or had a contraindication to β-blockers.

The C11 study included adult (≥18 years) patients (male or female, any ethnicity) with uni- or

bilaterally elevated IOP due to POAG or OH. Patients had to be taking: (i) β-blocker monotherapy for at least 4 weeks and have an IOP ≥22mm Hg; or (ii) adjunctive therapy and have an IOP <22mm Hg. After 2 weeks of monotherapy with timolol, patients had to have an IOP between 22 and 28mm Hg, inclusively. Patients with contraindications to β-blockers, sulfonamides, or α-agonists were excluded.

In the C14 and C15 studies, patients (male or female, any ethnicity) had to be ≥18 years of age and have uni- or bilaterally elevated IOP due to POAG or OH. After 4 weeks of monotherapy with brimonidine (C14) or dorzolamide (C15), patients had to have an IOP between 20 and 32mm Hg, inclusively, in each eligible eye. Patients with contraindications to α-agonists (C14) or sulfonamides (C15) were excluded.

The C12 study included healthy volunteers (male and female, 18 to 45 years of age, of any ethnicity) who successfully completed a treadmill test at screening without medical complications. The C13 study included patients (male and female, 18 to 70 years of age, of any ethnicity) with mild-to-moderate bronchial asthma; patients had to have a forced expiratory volume in one second (FEV_1) value ≥65% of predicted without the benefit of bronchodilators. Patients had to be in a stable respiratory state, with no change in asthma treatment for at least 4 weeks prior to entry, and have a history of reversible airflow obstruction.

1.2 Safety Variables and Analyses

In the two monotherapy studies, safety was based on ocular symptoms, best-corrected distance visual acuity, manifest refraction, dilated ophthalmoscopy, slit lamp biomicroscopy, visual fields, iris/eyelash photography, vital signs, and spontaneous reporting of adverse events. In the C4 study, safety was also based on specular microscopy and clinical laboratory data. In the three adjunctive therapy studies, safety was based on spontaneous reporting of adverse events, vital signs, and comprehensive ophthalmic examinations in all patients, including: ocular symptoms; best-corrected distance visual acuity; manifest refraction; ophthalmoscopy; slit lamp biomicroscopy; and visual fields.

In the mono- and adjunctive therapy studies, safety was assessed using all randomised patients. All statistical tests were two-sided, and tests with a corresponding p-value ≤0.050 were considered statistically significant. Fisher's exact test, the Kruskal-Wallis test, and the Wilcoxon rank sum test were used to analyse patient demographics and baseline disease characteristics, as appropriate. Changes from baseline in vital signs, visual acuity, endothelial cell count, cup-to-disc ratio, refractive error, iris colour luminescence, and eyelash density/length were tested within treatment using a paired t-test and between treatments using two-factor analysis of variance (ANOVA), with treatment and study centre as factors, as appropriate. Changes from baseline in other ophthalmic examinations and laboratory results were summarised using shift tables. Adverse event incidence was summarised by treatment. In the monotherapy studies, treatment-emergent adverse events were defined as those events that started or worsened after the initiation of monotherapy. In the adjunctive therapy studies, treatment-emergent adverse events were defined as those events that started or worsened after adjunctive therapy was initiated. For the purpose of analysis, adverse events were pooled for the monotherapy studies.

In the C12 study, heart rate was measured every minute during exercise and every 3 minutes during recovery; blood pressure was monitored every 2 and 3 minutes, respectively. Differences in exercise heart rate were analysed using a mixed model ANOVA, with effects for period, sequence, drug treatment, and carry-over. In C13, spirometric measurements were taken at pre-dose and again during a 4-hour period following drug instillation. Salbutamol (albuterol) 200μg was then administered by inhalation, and spirometry was repeated. The primary endpoint was the 4-hour post-dose weighted mean FEV_1, defined as the area under the

FEV_1 time curve divided by time. Secondary endpoints were the 4-hour post-dose weighted means for peak expiratory flow rate and forced vital capacity, peak change in FEV_1, maximum percentage change in FEV_1, and change in FEV_1 after bronchodilator challenge. Safety variables were analysed using a multi-factor ANOVA with effects for treatment, treatment sequence, and subject.

2. Safety of Unoprostone 0.15% as Monotherapy

2.1 Patient Demographics and Baseline Characteristics

In the C4 study, 571 patients received at least one dose of unoprostone 0.15% (379 patients) or timolol 0.5% (192 patients); mean duration of exposure was 294.7 days and 326.5 days in the unoprostone and timolol groups, respectively. In the C5 study, 560 patients were exposed to study drug, with 280 receiving unoprostone 0.15%, 139 receiving timolol 0.5%, and 141 receiving betaxolol 0.5%. Mean duration of exposure ranged from 341.0 days (unoprostone) to 353.4 days (timolol).

Approximately half of the patients in each monotherapy study were female, and most were Caucasian. Mean age was 60.6 years and 63.1 years in the C4 and C5 studies, respectively. The majority of patients in each study had brown- or blue-coloured irides. Duration of disease was approximately 5 years in the C4 study and 2 years in C5. Treatment groups were generally comparable with regard to demographic and baseline disease characteristics. The only statistically significant differences were observed in the C4 study for history of drug allergy/hypersensitivity (29% unoprostone, 42% timolol, $p = 0.004$) and distribution of iris colour ($p = 0.014$), mainly due to differences in the percentage of patients with hazel (16% unoprostone, 24% timolol) or blue (30% unoprostone, 21% timolol) eyes.

2.2 Adverse Events

As shown in table I, most of the patients in each treatment group experienced at least one adverse event (regardless of drug attribution) during the first 12 months of monotherapy (range: 76.1 to 81.2%). Most adverse events were mild or moderate in intensity and transient in duration. Approximately 6 to 9% of the patients in each treatment group experienced a serious adverse event (as defined by the US Food and Drug Administration) [table I]. Of these, four patients (taking unoprostone) died due to myocardial infarction, cardiac arrest, bladder carcinoma, or accidental injury. None of the deaths were attributed to study

Table I. Overall summary of adverse events (AEs) in the pooled monotherapy pivotal studies

Category	Percentage of patients		
	unoprostone 0.15% (n = 659)	timolol 0.5% (n = 331)	betaxolol 0.5% (n = 141)
One or more AEs	81.2	76.1	76.6
Ocular event	71.5	60.1	67.4
Non-ocular event	48.3	51.7	42.6
One or more drug-related[a] AEs	64.0	53.8	60.3
Ocular event	60.8	47.1	56.0
Non-ocular event	12.9	17.2	9.9
One or more serious[b] AEs	6.5	8.5	5.7
Deaths	0.6	0.0	0.0
Discontinued due to an AE[c]	6.8	5.7	3.5

a Considered by the investigator to be related or possibly related to study medication.

b As defined by the US Food and Drug Administration. This category includes serious AEs that resulted in death.

c Including deaths.

drug. Most of the serious events were systemic in nature. Only three patients had a serious ocular event, namely acute attack of angle-closure glaucoma (one timolol), worsening of cataract (one unoprostone), and endophthalmitis (one unoprostone). None of the serious ocular events were considered to be drug-related. Four patients had a serious systemic event attributed to study drug; these events were Bell's Palsy (one unoprostone), chest pain (one timolol), asthma and flu syndrome (one timolol), and congestive heart failure (one timolol).

Approximately 4 to 7% of the patients in each treatment group discontinued monotherapy due to an adverse event (drug-related or otherwise) [table I]. Across treatments, the most common events that led to discontinuation were abnormal vision, burning/stinging, and foreign body sensation (table II). Incidences of individual discontinuation events were low (≤1.1%) and comparable among treatments.

The majority of events (both overall and those attributed to study medication) were ocular in nature (table I). Across treatment groups, the most common drug-related adverse events were burning/ stinging (occurring throughout the day, not only upon instillation), burning/ stinging upon drug instillation (immediate sensation of burning/stinging directly upon instillation of the study drug), ocular itching, and conjunctival hyperaemia (table III). The incidence of drug-related burning/stinging was slightly higher in the unoprostone (24.1%) and betaxolol (24.8%) groups than in the timolol group (16.0%). The incidence of drug-related burning/ stinging upon drug instillation was also slightly higher in patients treated with unoprostone versus timolol or betaxolol (18.7, 12.4 and 12.8%, respectively).

Approximately 7 to 12% of the patients in each treatment group had drug-related ocular itching, and 6 to 11% had drug-related conjunctival hyperaemia (table III). Incidences of all other drug-related adverse events were ≤10% in each treatment group, with drug-related blepharitis, conjunctivitis, corneal lesion, ocular discharge, keratitis, and photophobia occurring in <4% of the patients in each group.

Incidences of drug-related systemic events were low and comparable among treatment groups, with headache being the most common event reported (2 to 3% per group) [table III]. Incidences of all other drug-related systemic events were ≤1% in each group.

Table II. Most common[a] adverse events resulting in discontinuation from either monotherapy pivotal study (pooled data)[b]

Adverse event	Percentage of patients		
	unoprostone 0.15% (n = 659)	timolol 0.5% (n = 331)	betaxolol 0.5% (n = 141)
At least one ocular event	3.0	1.2	2.1
Abnormal vision	1.1	0.9	0.0
Burning/stinging	0.6	0.3	0.0
Burning/stinging upon drug instillation	0.3	0.0	0.7
Conjunctivitis	0.5	0.0	0.0
Foreign body sensation	0.6	0.0	0.0
At least one non-ocular event	4.2	4.8	1.4
Asthma	0.2	0.6	0.0
Chest pain	0.2	0.6	0.0
Insomnia	0.3	0.3	0.0
Rash	0.5	0.0	0.0

a Events that led to discontinuation in more than two patients in all treatment groups combined.

b Including deaths.

Table III. Most common[a] drug-related[b] adverse events in the pooled monotherapy pivotal studies

Adverse event	Percentage of patients		
	unoprostone 0.15% (n = 659)	timolol 0.5% (n = 331)	betaxolol 0.5% (n = 141)
Ocular events			
Abnormal vision	7.0	5.7	2.8
Blepharitis	1.2	0.6	2.1
Burning/stinging	24.1	16.0	24.8
Burning/stinging upon drug instillation	18.7	12.4	12.8
Conjunctivitis	2.6	3.0	2.8
Corneal lesion	2.3	2.4	2.8
Discharge	2.3	1.8	0.0
Dry eyes	10.0	6.9	3.5
Eyelid disorder	5.0	4.2	7.1
Foreign body sensation	9.1	7.9	7.8
Injection (conjunctival hyperaemia)	11.2	10.3	5.7
Itching	12.1	10.0	7.1
Keratitis	2.6	0.9	0.0
Lacrimation disorder	7.6	6.3	5.0
Photophobia	3.9	3.0	0.7
Non-ocular events			
Headache	2.3	3.0	2.1

a Events that occurred in ≥2% of the patients in any treatment group.

b Considered by the investigator to be related or possibly related to study medication.

2.3 Other Examinations

None of the comprehensive ophthalmologic examination findings were clinically notable during the first 12 months of monotherapy. Only one patient (unoprostone) had a confirmed change in iris colour (i.e. darkening) at month 12. No clinically relevant differences were observed among treatments with respect to mean eyelash density or length. Overall, approximately 10 to 14% of patients from all treatment groups had an increase in eyelash length >1mm at month 12, whereas 7% had a decrease in eyelash length of similar magnitude. Four patients (two unoprostone, one timolol, one betaxolol) had abnormal eyelash growth reported as a drug-related treatment-emergent adverse event.

Mean changes from baseline in vital signs were not clinically relevant in patients treated with unoprostone. Small yet consistent mean decreases from baseline in heart rate were observed in patients treated with timolol; for the most part, however, these changes were not statistically significant. In patients treated with betaxolol, mean decreases from baseline were observed for each vital signs parameter throughout the evaluation period; although small, these changes were often statistically significant.

In the C4 study, most laboratory test results were within normal range at each evaluation, regardless of treatment. The percentage of patients who had a shift from normal at screening to abnormal at month 12 was comparable between treatments for each laboratory parameter.

3. Safety of Unoprostone 0.15% as Adjunctive Therapy

3.1 Patient Demographics and Baseline Characteristics

In the C11 study, 146 patients instilled at least one drop of unoprostone 0.15% (50 patients), dorzolamide 2.0% (48 patients), or brimonidine 0.2% (48 patients) as adjunctive therapy to timolol 0.5%. Duration of exposure to adjunctive therapy ranged from 81.3 days (unoprostone) to 82.3 days (dorzolamide). Forty-three patients were exposed to adjunctive therapy during the C14/C15 studies (21 unoprostone, 22 placebo). Median duration of exposure was 28 days for each drug combination.

At least half of the patients in each adjunctive therapy study were female, and most, if not all, were Caucasian. Mean age ranged from 62.0 years (C15) to 66.1 years (C14). Across studies, the most common iris colours were blue and brown. Mean duration of disease was approximately 6 years in the C11 study and 7 years in the C14/C15 studies. In each study, demographics and baseline disease characteristics were comparable among treatments; no statistically significant differences were observed, except for the percentage of patients in C14 who had a coexistent ocular condition (55% placebo, 100% unoprostone, $p = 0.035$).

3.2 Adverse Events

In the C11 study, the percentage of patients who experienced at least one treatment-emergent adverse event (regardless of drug attribution) was generally comparable among treatment groups (range: 27.1 to 35.4%), with the highest incidence occurring in patients treated adjunctively with dorzolamide (table IV). Most adverse events were mild or moderate in intensity and transient in duration. Six patients (three unoprostone, three dorzolamide) experienced a serious adverse event during adjunctive therapy. Of these, one patient (dorzolamide) died due to myocardial infarction unrelated to study treatment. Serious events attributed to study medication were personality disorder (one unoprostone), corneal lesion (one unoprostone), and retinal artery occlusion (one dorzolamide). Approximately 4 to 8% of the patients in each treatment group discontinued adjunctive therapy due to a treatment-emergent adverse event (drug-related or otherwise) [table IV]. The majority of discontinuation events were systemic in nature. The only event that resulted in withdrawal in more than one patient was tachycardia (one dorzolamide, one brimonidine).

Across treatment groups, the majority of drug-related treatment-emergent events were ocular in

Table IV. Overall summary of treatment-emergent adverse events (AEs) in the largest adjunctive therapy study (C11)

Category	Percentage of patients		
	timolol + unoprostone (n = 50)	timolol + dorzolamide (n = 48)	timolol + brimonidine (n = 48)
One or more AEs	30.0	35.4	27.1
Ocular event	20.0	25.0	12.5
Non-ocular event	12.0	25.0	18.8
One or more drug-related[a] AEs	22.0	29.2	22.9
Ocular event	18.0	22.9	10.4
Non-ocular event	4.0	16.7	14.6
One or more serious[b] AEs	6.0	6.3	0.0
Deaths	0.0	2.1	0.0
Discontinued due to an AE[c]	6.0	8.3	4.2

a Considered by the investigator to be related or possibly related to study medication.

b As defined by the US Food and Drug Administration. This category includes serious AEs that resulted in death.

c Including deaths.

Table V. Most common[a] drug-related[b] adverse events in the largest adjunctive therapy study (C11)

Adverse event	Percentage of patients		
	timolol + unoprostone (n = 50)	timolol + dorzolamide (n = 48)	timolol + brimonidine (n = 48)
Ocular events			
Abnormal vision	0.0	0.0	4.2
Burning/stinging	4.0	14.6	4.2
Burning/stinging upon drug instillation	8.0	2.1	0.0
Foreign body sensation	4.0	0.0	4.2
Itching	0.0	0.0	8.3
Lacrimation disorder	2.0	4.2	2.1
Non-ocular events			
Dry mouth	0.0	4.2	2.1
Headache	0.0	2.1	4.2
Hypertension	0.0	0.0	4.2
Nausea	0.0	4.2	0.0
Tachycardia	0.0	4.2	2.1
Taste perversion	0.0	4.2	0.0
Vertigo	0.0	6.3	2.1

a Treatment-emergent events that occurred in >4% of the patients in any treatment group during adjunctive therapy.

b Considered by the investigator to be related or possibly related to study medication.

nature, with the most common being burning/stinging and burning/stinging upon instillation (table V). The incidence of drug-related burning/stinging was higher in patients adjunctively treated with dorzolamide (14.6%) versus brimonidine (4.2%) or unoprostone (4.0%), whereas the incidence of drug-related burning/stinging upon instillation was highest in patients adjunctively treated with unoprostone (8.0 *vs* 2.1% and 0.0% for dorzolamide and brimonidine, respectively). The only cases of drug-related treatment-emergent ocular itching occurred in patients who received brimonidine as adjunctive therapy (8.3%). Incidences of all other drug-related treatment-emergent events were ≤6.3% in each treatment group. Unlike the other adjunctive therapies, none of the drug-related treatment-emergent systemic events occurred in patients adjunctively treated with unoprostone.

In the C14/C15 studies, adverse event profiles were nearly identical between unoprostone and placebo. All but one treatment-emergent adverse event was mild or moderate in intensity, and none were classified as serious or led to discontinuation of adjunctive therapy.

In the C14 study, approximately 55% of the patients in each treatment group experienced at least one adverse event during adjunctive therapy, the majority of which were attributed to study drug (36.4% placebo, 45.5% unoprostone). Distributions of drug-related ocular events were comparable between treatments (27.3% per group), as were drug-related systemic events (18.2% placebo, 27.3% unoprostone). Drug-related adverse events that occurred in more than one patient were asthenia (one placebo, one unoprostone), conjunctivitis (two placebo, two unoprostone), headache (one placebo, one unoprostone), and ocular itching (two placebo).

In the C15 study, the majority of patients in each treatment group experienced at least one adverse event during adjunctive therapy (63.6% placebo, 70.0% unoprostone), most of which were attributed to study drug (54.5% placebo, 50.0%

unoprostone) and ocular in nature (45.5% placebo, 50.0% unoprostone). The only drug-related adverse events that occurred in more than one patient were blepharitis (two placebo, one unoprostone) and conjunctival hyperaemia (two placebo, two unoprostone).

3.3 Other Examinations

In each adjunctive therapy study, none of the comprehensive ophthalmic examination findings were indicative of a safety concern. Furthermore, adjunctive therapy appeared to have no clinically relevant effect on vital signs.

4. Safety of Unoprostone 0.15% in Special Populations

In the C12 study, 30 healthy volunteers were exposed to study drug. Overall, extent of exposure was 145 subject-days for unoprostone 0.15%, 144 subject-days for timolol 0.5%, and 135 subject-days for placebo. Approximately half of the patients were female, and most were Caucasian; mean age was 24.1 years. At each timepoint during the exercise and recovery periods, unoprostone and placebo were comparable with regard to change in exercise-induced heart rate; no clinically or statistically significant treatment differences were observed. In contrast, timolol significantly ($p < 0.05$) suppressed increases in exercise-induced heart rate at each timepoint during the evaluation periods relative to placebo and at all but one timepoint relative to unoprostone.

In the C13 study, 16 patients received a single drop of unoprostone 0.15% and placebo in both eyes, with a 3-day washout between treatments. All patients were Caucasian, and the majority were male; mean age was 43 years. The 4-hour post-dose weighted mean FEV_1 was 2.70L with unoprostone and 2.77L with placebo. This difference was not clinically or statistically significant. Other spirometric and symptomatic evaluations were consistent with the primary assessment. No difference was observed between treatments with regard to reversibility of bronchoconstriction following bronchodilator challenge.

5. Safety of Unoprostone 0.12% as Monotherapy

Several publications have reported on the safety of unoprostone 0.12% as monotherapy. In two Japanese phase II studies, unoprostone (0.006, 0.03, 0.06 or 0.12%) had no effect on pupil diameter, visual acuity, visual field, slit lamp microscopy, colour perception, or funduscopy after 3 to 4 weeks of therapy in 173 patients with POAG or OH.[9,16] Most patients in each study had no adverse effects. Except for one case of mild headache, no systemic adverse events were reported. Ocular events were mild and transitory, and none required treatment or withdrawal of drug. In a phase III double-blind comparative study, neither unoprostone 0.12% nor timolol 0.5% had any clinically notable effects on visual acuity, visual field, anterior chamber angle, funduscopy, pupil diameter, or laboratory safety after 12 weeks of therapy in 158 Japanese patients with POAG or OH.[10] Most (≥93%) patients in each group had no adverse effects. Adverse events consisted of conjunctival hyperaemia (4% per group), conjunctival folliculosis (1% unoprostone), burning sensation (1% unoprostone), headache (1% unoprostone), nausea/vomiting (1% unoprostone), nasal congestion (1% unoprostone), dizziness (1% timolol), and temporary unconsciousness (1% timolol). None of the adverse events required treatment or cessation of drug. Unoprostone had no effect on vital signs, whereas timolol caused significant reductions in blood pressure; two timolol-treated patients also had sustained bradycardia.

In a long-term study, unoprostone was well tolerated in 114 Japanese patients with POAG or OH who instilled unoprostone 0.06% or 0.12% twice daily for 52 weeks.[32] Adverse events reported with either concentration were conjunctival hyperaemia (9%), corneal erosion (4%), blepharitis (1%), miscellaneous (unspecified) ocular events (5%), headache (2%), dry mouth (1%), and pares-

thesia (1%). Only one (1%) patient discontinued drug due to an adverse event (unspecified). No changes in iris pigmentation were observed. Unoprostone 0.12% had no clinically relevant effect on visual acuity, visual field, or cup-to-disc ratio in 13 Japanese patients with low tension glaucoma who instilled drug twice daily for 6 months.[11] Shimazaki et al.[33] reported that unoprostone 0.12% had no adverse effects on corneal epithelial integrity or tear function after 6 months of therapy, whereas timolol significantly impaired both tear production and turnover.

Nordmann et al.[34] reported similar safety profiles for unoprostone 0.12% and timolol 0.5% after 6 weeks of therapy in 40 non-Asian patients. No clinically relevant decreases in visual acuity or changes in pupil size were observed. Drug tolerability was rated as good to excellent for both medications. Mild and transient burning upon instillation occurred in both groups, although more frequently with unoprostone. In a study of 36 non-Asian patients, unoprostone 0.12% instilled two or three times daily had a comparable safety profile to timolol 0.5% after 2 weeks of therapy.[35] No differences in ophthalmic examinations were noted. Adverse effects consisted of sore eyelids (4% unoprostone), uveitis (8% timolol), nausea (13% unoprostone), headache (4% unoprostone, 8% timolol), fractured ribs (4% unoprostone), and urinary tract infection (8% timolol). Except for uveitis (timolol), none of the events caused discontinuation of drug.

6. Safety of Unoprostone 0.12% as Adjunctive Therapy

Several studies have demonstrated the safety of unoprostone 0.12% as adjunctive therapy to other IOP-lowering medications, such as β-blockers (e.g. timolol, carteolol),[8,12,13,36] pilocarpine,[8,12,13,37] carbonic anhydrase inhibitors (e.g. acetazolamide),[8,12,13] latanoprost,[19] and dipivefrin.[8,12] In one study, 15 Japanese patients with refractory glaucoma or OH instilled unoprostone 0.12% as adjunctive therapy to β-blockers, pilocarpine, dipivefrin, and/or carbonic anhydrase inhibitors over a 12-week period.[8] Adverse effects attributed to treatment were conjunctival hyperaemia, watery eyes, light sensitivity, and localised stinging (one patient each); all were mild and transient in duration. No adverse effects were reported in patients who continued adjunctive therapy up to 12 months. In another study,[12] 39 Japanese patients with severe refractory glaucoma instilled unoprostone 0.12% as adjunctive therapy to β-blockers, pilocarpine, dipivefrin, and/or carbonic anhydrase inhibitors for 12 weeks or longer. Addition of unoprostone had no effect on any ophthalmic examination, including pupil diameter, visual acuity, visual field, and funduscopy. Most (82%) patients had a high overall safety rating with no adverse effects. No systemic adverse events attributed to therapy were reported. Drug-related ocular events were stinging (13%), conjunctival hyperaemia (10%), foreign body sensation (3%), corneal erosion (3%), and eyelid dermatitis (3%). Two (5%) patients discontinued due to severe stinging or dermatitis.

Except for mild and transient stinging, no adverse effects were reported in 10 Japanese patients with glaucoma or OH who added unoprostone 0.12% to their existing therapy (timolol, pilocarpine, and/or an oral carbonic anhydrase inhibitor) for 12 weeks.[13] Yamamoto et al.[37] reported no abnormalities in ten Japanese patients with POAG or OH who instilled unoprostone 0.12% as adjunctive therapy to pilocarpine over a 2-week period. Two patients experienced mild eye pain or feeling of darkness, both of which were attributed to pilocarpine. In another Japanese study, no notable adverse effects were reported after 12 weeks of combination therapy with unoprostone 0.12% and timolol in seven patients with POAG or OH.[36]

In a non-Asian study,[19] 41 patients with POAG or OH instilled unoprostone 0.12% or placebo as adjunctive therapy to latanoprost over an 8-week period. Unoprostone-treated patients experienced hyperaemia (33%), stinging upon instillation (33%), punctate epithelial erosion (24%), foreign

body sensation (5%), burning sensation (5%), and visual field restriction at night (5%); no systemic adverse events were noted. Except for stinging upon instillation (0% placebo; 33% unoprostone), unoprostone was comparable to placebo. None of the patients discontinued adjunctive therapy due to an adverse event. No cases of uveitis, cystoid macular oedema, or conjunctival hyperaemia were observed over latanoprost alone.

7. Discussion

Since glaucoma is a chronic and progressive disease requiring long-term therapy, safety of glaucoma medications is of utmost importance. Furthermore, to promote compliance and continued use, these medications must be well tolerated. This overview describes the safety and tolerability of unoprostone, both at the 0.12% concentration, as described in the literature (mainly from Japanese regulatory trials), and for the newly-approved 0.15% formulation, based on results of US and European regulatory trials.

The safety profile presented in this review for unoprostone 0.15% is consistent with published information on unoprostone 0.12%, both as mono- and adjunctive therapy. Pooled results from the long-term (12 months) pivotal studies show that unoprostone 0.15% monotherapy has an excellent safety profile and is well tolerated in non-Asian patients with POAG or OH. Ocular safety examinations did not show any notable effects of unoprostone 0.15% on visual acuity, manifest refraction, dilated ophthalmoscopy, slit-lamp biomicroscopy, visual fields, or mean eyelash density/length. Iris colour change (i.e. darkening) was confirmed in one of 659 patients treated with unoprostone 0.15% after 12 months of therapy.[28]

Most adverse events observed in unoprostone-treated patients were mild or moderate in intensity and transient in nature. Less than 7% of unoprostone patients discontinued monotherapy due to an adverse event, mainly due to systemic events unrelated to treatment. The most common adverse events associated with unoprostone 0.15% monotherapy were (in descending order) burning/stinging, burning/stinging upon drug instillation, ocular itching, and conjunctival hyperaemia. Although common, most cases of burning/stinging and burning/stinging upon instillation were mild and transient in duration, and only a few cases warranted cessation of therapy. Burning/stinging, particularly upon instillation, is a common complaint with topical glaucoma medications.

Unoprostone 0.15% also exhibited an excellent profile in terms of systemic safety, with relatively few systemic events reported and no clinically relevant effects on laboratory safety or vital signs. Unlike timolol, unoprostone did not attenuate increases in exercise-induced heart rate in healthy subjects, indicating a lack of effect on systemic β-adrenergic receptors. Unoprostone also had no deleterious effects on pulmonary function in mild-to-moderate asthmatics.

Results of the short-term (≤3 months) adjunctive therapy studies demonstrate that unoprostone 0.15% has an excellent safety profile and is well tolerated as adjunctive therapy to timolol, brimonidine, and dorzolamide. The safety of unoprostone 0.15% as adjunctive therapy closely resembles that described for monotherapy, suggesting no additional risk to patients who require more than one IOP-lowering medication.

Since the Japanese launch of unoprostone 0.12% in 1994, unoprostone has been used in more than 30 countries around the world. Estimated exposure is over 500 000 patients through December 2000. Postmarketing surveys conducted over a 6.5 year period support the lack of safety concerns with unoprostone as observed in clinical trials.[38]

Collectively, the information presented herein shows that unoprostone has an excellent safety and tolerability profile. Furthermore, except for mild and transient burning/stinging, unoprostone safety is comparable, if not superior, to other glaucoma therapies. Unlike β-blockers (e.g. timolol[39]), unoprostone is not contraindicated in patients with impaired cardiovascular or pulmonary function and is not associated with a high incidence of clinical

depression or hyperlipaemia. Potential drug interactions also exist between topical β-blockers and other medications, including oral β-blockers, calcium channel blockers, and catecholamine-depleting agents. Unoprostone is not associated with bitter taste, anorexia, electrolyte abnormalities, renal calculi, or blood dyscrasias as observed with carbonic anhydrase inhibitors (e.g. dorzolamide[40]), nor is it contraindicated in patients with sensitivity to sulfonamides. Several events (i.e. ocular allergy, dry mouth, fatigue/drowsiness) associated with α_2-adrenergic agonists such as brimonidine[41] occur infrequently with unoprostone. The docosanoid unoprostone is not associated with a high incidence of topical allergic reaction as with adrenergic agonists (e.g. topical epinephrine) or with myopia and miosis observed with parasympathetic drugs such as pilocarpine. Unoprostone and latanoprost[42] generally have similar safety and tolerability profiles, although eyelash hypertrichosis and hyperpigmentation of the iris, eyelid, and eyelashes appear to occur more frequently with latanoprost. In pivotal trials, the incidence of iris colour change was very low (0.15%) after 12 months of therapy with unoprostone 0.15%.[28] Few cases have been reported in the literature with unoprostone [43] or through postmarketing surveillance.[38] With latanoprost, iris colour change occurs in 3 to 10% of patients treated for 6 months[44-46] and in 11 to 23% of patients after 12 months of therapy.[47]

8. Conclusions

In summary, unoprostone instilled twice daily has an excellent safety profile in patients with POAG or OH, both as monotherapy and as adjunctive therapy to other glaucoma medications. Furthermore, the safety of unoprostone is comparable, if not superior, to the safety of other glaucoma agents. This is not surprising in light of its similarity to naturally occurring metabolites, the docosanoids, of a widely distributed fatty acid, docosahexaenoic acid in the body. Unoprostone is the first docosanoid-type drug to gain US approval in patients with POAG or OH. It provides a unique and valuable option for the physiological management of glaucoma, particularly in patients who are intolerant of or insufficiently responsive to other therapies. Unoprostone may also be safely used in patients with impaired cardiovascular or pulmonary function, making it a viable alternative when β-blockers are contraindicated.

Acknowledgements

The authors acknowledge the medical writing assistance of Joan C. Rivers, Ph.D., with Diamond Communications & Research, Inc. (Rabun Gap, Georgia, USA).

This publication was sponsored by Novartis Ophthalmics, the manufacturer of unoprostone isopropyl (Rescula®) in the US and Europe.

References

1. Nishi A, Emi K, Ito Y, et al. Effect of topical application of Rescula® on ocular circulation [in Japanese]. J Eye 1996; 13: 1422-4
2. Nishimura T, Okamoto N. Effect of isopropyl unoprostone (Rescula®) topical administration on ophthalmic blood velocity in patients with normal-tension glaucoma [in Japanese]. J Eye 1998; 15: 281-4
3. Sugiyama T, Tokuoka S, Nakashima M, et al. Changes in rabbit capillary blood flow and corneal temperature with topically applied UF-021, bunazosin hydrochloride and propranolol hydrochloride [in Japanese]. J Eye 1992; 9 (8): 1430-4
4. Sugiyama T, Azuma I. Effect of UF-021 on optic nerve head circulation in rabbits. Jpn J Ophthalmol 1995; 39 (2): 124-9
5. Ogo T. Effect of isopropyl unoprostone on choroidal circulation: changes in choroidal blood flow and intraocular pressure with topical application. Ganka 1996; 47 (8): 268-72
6. Kojima S, Sugiyama T, Azuma I, et al. Effect of topically applied isopropyl unoprostone on microcirculation in the human ocular fundus evaluated with a laser speckle microcirculation analyser. Nippon Ganka Gakkai Zasshi 1997 Jul; 101 (7): 605-10
7. Makimoto Y, Sugiyama T, Kojima S, et al. Long-term effect of topically applied isopropyl unoprostone on microcirculation in the choroid-retina. Nippon Ganka Gakkai Zasshi 2000 Jan; 104 (1): 39-43
8. Azuma I. Clinical evaluation of UF-021 ophthalmic solution in glaucoma patients refractory to maximum tolerable therapy. Nippon Ganka Gakkai Zasshi 1993 Feb; 97 (2): 232-8
9. Azuma I, Masuda K, Kitazawa K, et al. Phase II double-masked dose-determination study of UF-021 (Rescula®) ophthalmic solution in primary open-angle glaucoma and ocular hypertension. Ganka 1992; 43: 1425-31
10. Azuma I, Masuda K, Kitazawa Y, et al. Double-masked comparative study of UF-021 and timolol ophthalmic solutions in patients with primary open-angle glaucoma or ocular hypertension. Jpn J Ophthalmol 1993; 37 (4): 514-25
11. Fujimori C, Yamabayashi S, Hosoda M, et al. The clinical evaluation of UF-021, a new prostaglandin related compound, in

low tension glaucoma patients. Nippon Ganka Gakkai Zasshi 1993 Oct; 97 (10): 1231-5
12. Motegi Y, Araie M, Suzuki Y, et al. Clinical study of UF-021 (Rescula®) ophthalmic solution in refractory glaucoma. Ganki 1993; 44 (1): 12-8
13. Shiose Y. Clinical study of UF-021 (Rescula®) ophthalmic solution, a novel metabolite-type prostaglandin for the treatment of glaucoma and ocular hypertension [in Japanese]. J Eye 1993; 10 (10): 1761-7
14. Takase M, Murao M, Koyano S, et al. Ocular effects of topical instillation of UF-021 ophthalmic solution in healthy volunteers. Nippon Ganka Gakkai Zasshi 1992; 96 (10): 1261-7
15. Takase M, Murao M, Koyano S, et al. Ocular effects of continuous topical instillations of UF-021 ophthalmic solution in healthy volunteers [in Japanese]. J Eye 1992; 9 (6): 1055-9
16. Takase M, Nanba H, Kato M, et al. Early phase II clinical study of UF-021 ophthalmic solution in primary open-angle glaucoma or ocular hypertension patients [in Japanese]. J Eye 1992; 9 (11): 1917-25
17. Sharpe ED, Kapik B, Reaves A, et al. Comparison of the effect of different concentrations of the docosanoid unoprostone isopropyl on intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension [abstract]. Invest Ophthalmol Vis Sci 2001 Mar; 42 (4): S822
18. Hommer A, Kapik B, Shams N. Unoprostone as adjunctive therapy to timolol: a double-masked randomized study versus brimonidine and dorzolamide. Br J Ophthalmol. In press
19. Stewart WC, Sharpe ED, Stewart JA, et al. Additive efficacy of unoprostone isopropyl 0.12% (Rescula®) to latanoprost 0.005%. Am J Ophthalmol 2001; 131 (3): 339-44
20. Nordmann J-P, Mertz B, Yannoulis NC, et al. A double-masked randomized comparison of the efficacy and safety of unoprostone with timolol and betaxolol in patients with primary open-angle glaucoma (including pseudoexfoliation glaucoma), or ocular hypertension. 6 Month Data. Am J Ophthalmol 2002; 133: 1-10
21. Questel I, Pages C, Lambrou GN, et al. Effects of unoprostone isopropyl in ocular blood flow decrease induced by systemic vasoconstrictor administration in cynomolgus monkeys [abstract]. Invest Ophthalmol Vis Sci 2000; 41 (4): S560
22. Yu DY, Su EN, Cringle SJ, et al. Comparison of the vasoactive effects of the docosanoid unoprostone and selected prostanoids on isolated perfused retinal arterioles. Invest Ophthalmol Vis Sci 2001 Mar; 42 (7): 1499-504
23. Polska E, Doelemeyer A, Luksch A, et al. Partial antagonism of endothelin 1-induced vasoconstriction in the human choroid by topical unoprostone isopropyl. Arch Ophthalmol 2002 Mar; 120 (3): 348-52
24. LaFuente MP, Mayor-Torroglosa S, Villagas-Perez M, et al. Retinal ganglion cell survival after transient ligation of the ophthalmic vessels and administration of unoprostone isopropyl. [ARVO abstract]. Invest Ophthalmol Vis Sci 2000 Mar; 41 (4): S15
25. Marcheselli VL, DeCoster MA, Campbell Z, et al. Neuroprotection by unoprostone, but not by latanprost, against glutamate-stimulated calcium influx and cell death in retinal ganglion cells. [ARVO abstract]. Invest Ophthalmol Vis Sci 2001 Mar; 42 (4): S750
26. Hiida Y, Kishimoto N, Deguchi T. Protective effects against light damage to the photoreceptor by topical application with isopropyl unoprostone ophthalmic solution [ARVO abstract]. Invest Ophthalmol Vis Sci 1999; 40 (4): S953
27. Altman B, Craven ER, Shams NBK, et al. Safety of the docosanoid unoprostone isopropyl 0.15% when used adjunctively with brimonidine tartrate 0.2% or dorzolamide HCl 2.0% in patients with primary open-angle glaucoma or ocular hypertension [abstract]. Invest Ophthalmol Vis Sci 2001 Mar; 42 (4): S417
28. Melamed S, Nordmann J, Yannoulis N, et al. The efficacy and safety of unoprostone isopropyl 0.15%, timolol maleate 0.5%, and betaxolol hydrochloride 0.5% in patients with primary open-angle glaucoma or ocular hypertension: month 12 data [abstract]. Invest Ophthalmol Vis Sci 2001 Mar; 42 (4): S556
29. Stewart WC, Stewart JA, Crockett S, et al. Comparison of the cardiovascular effects of unoprostone 0.15%, timolol 0.5%, and placebo in healthy adults during exercise using a treadmill test. Acta Ophthalmol Scand 2002; 80: 272-6
30. Stewart WC, Mundorf T, Haque RM, et al. Comparison of the IOP-lowering efficacy and safety of the docosanoid unoprostone isopropyl 0.15% versus timolol maleate 0.5% dosed twice daily for 6 months in patients with primary open-angle glaucoma or ocular hypertension [abstract]. Invest Ophthalmol Vis Sci 2001 Mar; 42 (4): S557
31. Gunewardena KA, Crame N, Mertz B, et al. Safety of unoprostone isopropyl 0.15% ophthalmic solution in patients with mild-to-moderate asthma. Ophthalmologica. In press.
32. Yamamoto T, Kitazawa Y, Azuma I, et al. Clinical evaluation of UF-021 (Rescula®; isopropyl unoprostone). Surv Ophthalmol 1997; 41 Suppl. 2: S99-103
33. Shimazaki J, Hanada K, Yagi Y, et al. Changes in ocular surface caused by antiglaucomatous eyedrops: prospective, randomised study for the comparison of 0.5% timolol *vs* 0. 12% unoprostone. Br J Ophthalmol 2000 Nov; 84 (11): 1250-4
34. Nordmann JP, Rouland JF, Mertz BP. A comparison of the intraocular pressure-lowering effect of 0.5% timolol maleate and the docosanoid derivative of a PGF2 alpha metabolite, 0.12% unoprostone, in subjects with chronic open-angle glaucoma or ocular hypertension. Curr Med Res Opin 1999; 15 (2): 87-93
35. Stewart WC, Stewart JA, Kapik BM. The effects of unoprostone isopropyl 0. 12% and timolol maleate 0.5% on diurnal intraocular pressure. J Glaucoma 1998 Dec; 7 (6): 388-94
36. Nakamatsu T, Okinami S, Oono S. The ocular hypotensive effect of concomitant use of isopropyl unoprostone (Rescula®) and timolol [in Japanese]. J Eye 1996; 13 (3): 439-41
37. Yamamoto T, Chi Q, Kitazawa Y. Interaction between a prostaglandin F2 alpha derivative, UF-021, and pilocarpine in ocular hypotensive therapy. Nippon Ganka Gakkai Zasshi 1994; 98 (2): 202-5
38. Data on file, Novartis Ophthalmics
39. Package insert for Timoptic® 0. 25% and 0.5%. Physician's desk reference for ophthalmology. Montvale (NJ): Medical Economics Company, 2001; 29: 294-7
40. Package insert for Trusopt® 2. 0%. Physician's desk reference for ophthalmology. Montvale (NJ): Medical Economics Company, 2001; 29: 303-4
41. Package insert for Alphagan® 0. 2%, in: Physician's desk reference for ophthalmology. Montvale (NJ): Medical Economics Company, 2001; 29th ed.: 229-30

42. Package insert for Xalatan™ 0. 005%. Physician's desk reference for ophthalmology. Montvale (NJ): Medical Economics Company, 2001; 29: 315-7
43. Yamamoto T, Kitazawa Y. Iris-color change developed after topical isopropyl unoprostone treatment. J Glaucoma 1997; 6 (6): 430-2
44. Alm A, Stjernschantz J, and the Scandinavian Latanoprost Study Group. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning: a comparison with timolol. Ophthalmology 1995; 102: 1743-52
45. Camras CB, the United States Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. Ophthalmology 1996; 103: 138-47
46. Watson P, Stjernschantz J, and the Latanoprost Study Group. A six-month, randomized double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. Ophthalmology 1996; 103: 126-37
47. Wistrand PJ, Stjernschantz J, Olsson K. The incidence and time-course of latanoprost-induced iridial pigmentation as a function of eye color. Surv Ophthalmol 1997; 41 Suppl. 2: S129-38

Correspondence and offprints: Dr *Reza M. Haque*, Novartis Ophthalmics, Inc., 11695 Johns Creek Parkway, Duluth, GA 30097, USA.
E-mail: reza.haque@pharma.novartis.com