

Medicines Adverse Reactions Committee

Meeting date	9/06/2022	Agenda item	3.2.3
Title	Prostaglandin associated periorbitopathy		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	Product name*	Sponsor	
Bimatoprost	Bimatoprost Multichem Eye drops, solution, 0.3 mg/mL	Multichem NZ Limited	
	Latisse Topical solution, 0.3 mg/mL, Allergan	Allergan New Zealand Ltd	
	Lumigan Eye drops, solution, 0.3 mg/mL	Allergan New Zealand Ltd	
	Lumigan PF Eye drops, solution, 0.3 mg/mL	Allergan New Zealand Ltd	
Bimatoprost; timolol	Ganfort PF 0.3/5 Eye drops, solution, 300mcg/mL & 5mg/mL	Allergan New Zealand Ltd	
	Ganfort® 0.3/5 Eye drops, solution	Allergan New Zealand Ltd	
Latanoprost	Latanoprost Eye drops, solution, 50 mcg/mL, Teva	Teva Pharma (New Zealand) Limited	
Latanoprost; timolol	Arrow - Lattim Eye drops, solution, 0.05mg/mL, 5mg/mL	Teva Pharma (New Zealand) Limited	
Travoprost	Travatan Eye drops, solution, 0.004 %, PQ Eye Drops	Novartis New Zealand Ltd	
Travoprost; timolol	DuoTrav Eye drops, solution, 40 micrograms/mL, 5 mg/mL	Novartis New Zealand Ltd	
* the prostaglandin analogues included above are those for ocular administration with a status of consent given at April 2022.			
PHARMAC funding	The following medicines are funded on the pharmaceutical schedule and hospital medicines list: <ul style="list-style-type: none"> • Bimatoprost Multichem (bimatoprost) • Latanoprost Teva (latanoprost) • Arrow Lattim (latanoprost with timolol) • Travatan (travoprost) 		
Previous MARC meetings	Prostaglandin analogues have not been discussed at a previous MARC meeting.		
International action	At the 29-31 October 2018 meeting, the Pharmacovigilance Risk Assessment Committee (PRAC) requested Marketing Authorisation Holders to provide a cumulative review on PAP-related adverse events with bimatoprost treatment in the next Periodic Benefit Risk Evaluation Report (PBRER). Bimatoprost was discussed at the 8 – 11 November 2021 meeting of the United Kingdom Committee for medicinal products for human use (CHMP) . The CHMP recommended the following changes:		

	<p>Update of section 4.4 and 4.8 of the SmPC to add the adverse reaction prostaglandin analogue periorbitopathy with a frequency very common. The Package leaflet is updated accordingly.</p> <p>See section 2.4 for further information.</p>																																				
<i>Prescriber Update</i>	No related articles have been published in <i>Prescriber Update</i> to date.																																				
Classification	Prescription medicine																																				
Usage data	<p>The tables below show the number of people (NumPpl) who received a dispensing of bimatoprost, latanoprost or travoprost from a pharmacy at least once during the specified year. Data source is the Ministry of Health's Pharmaceutical Collection, extracted on 26 November 2021.</p> <p><u>Bimatoprost</u></p> <table border="1"> <thead> <tr> <th>Year</th> <th>NumPpl</th> </tr> </thead> <tbody> <tr> <td>2016</td> <td>7844</td> </tr> <tr> <td>2017</td> <td>7708</td> </tr> <tr> <td>2018</td> <td>7534</td> </tr> <tr> <td>2019</td> <td>7236</td> </tr> <tr> <td>2020</td> <td>7083</td> </tr> </tbody> </table> <p><u>Latanoprost</u></p> <table border="1"> <thead> <tr> <th>Year</th> <th>NumPpl</th> </tr> </thead> <tbody> <tr> <td>2016</td> <td>26523</td> </tr> <tr> <td>2017</td> <td>27414</td> </tr> <tr> <td>2018</td> <td>28670</td> </tr> <tr> <td>2019</td> <td>29630</td> </tr> <tr> <td>2020</td> <td>30063</td> </tr> </tbody> </table> <p><u>Travoprost</u></p> <table border="1"> <thead> <tr> <th>Year</th> <th>NumPpl</th> </tr> </thead> <tbody> <tr> <td>2016</td> <td>4028</td> </tr> <tr> <td>2017</td> <td>3952</td> </tr> <tr> <td>2018</td> <td>3849</td> </tr> <tr> <td>2019</td> <td>3762</td> </tr> <tr> <td>2020</td> <td>3669</td> </tr> </tbody> </table>	Year	NumPpl	2016	7844	2017	7708	2018	7534	2019	7236	2020	7083	Year	NumPpl	2016	26523	2017	27414	2018	28670	2019	29630	2020	30063	Year	NumPpl	2016	4028	2017	3952	2018	3849	2019	3762	2020	3669
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Advice sought	<p>The Committee is asked to advise:</p> <ul style="list-style-type: none"> • whether the risk of prostaglandin associated periorbitopathy is a class effect • if yes, whether the risk differs across the class • whether any communication, other than MARCs Remarks is required. 																																				

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1 PURPOSE

This paper is being presented to the Medicines Adverse Reactions Committee (MARC) following a sponsor notification of regulatory activity in the United Kingdom regarding bimatoprost and prostaglandin associated periorbitopathy (PAP).

Product information for medicines containing bimatoprost have recently been updated in the United Kingdom to include the risk of PAP.

Bimatoprost, latanoprost and travoprost are prostaglandin analogues.

The purpose of this paper is to seek advice from the MARC on whether this is a class effect and if yes, whether the risk differs across the class.

2 BACKGROUND

The Pharmacovigilance Risk Assessment Committee (PRAC) provided a recommendation to the Committee for Medicinal Products for Human Use (CHMP), in November 2021, that the product information for bimatoprost should be updated to add the adverse reaction of PAP. The CHMP agreed with the recommendation and requested companies update their product information. Product information in the UK for bimatoprost containing products now includes information on PAP. The UK and European product information uses the term 'prostaglandin analogue periorbitopathy' rather than prostaglandin associated periorbitopathy'. The slightly different terms seem to be used for the same general condition. For consistency, prostaglandin associated periorbitopathy has been used throughout this report.

Medsafe recommends that data sheets for products containing bimatoprost in New Zealand should also be updated with similar wording regarding the risk of PAP (see section 2.4). As mentioned above, Medsafe would like to seek advice from the MARC on whether this should extend to other prostaglandin analogues.

2.1 Prostaglandin analogues

Prostaglandin analogues are a class of medicines that bind to a prostaglandin receptor and have several uses. They are commonly used to treat glaucoma but prostaglandin analogues can also treat stomach ulcers, pulmonary hypertension and induce labour [1-3].

This report only considers the prostaglandin analogues listed on the first page as they have been identified as medicines for ocular use and are approved in New Zealand.

In glaucoma, prostaglandin analogues are successful at lowering intraocular pressure with a relative lack of systemic side effects [4]. This has led to them becoming a popular first-line treatment [4].

2.1.1 Bimatoprost

Bimatoprost is a synthetic analogue of prostaglandin and decreases intraocular pressure by increasing the outflow of aqueous humour [5]. Eye drops containing bimatoprost are indicated as monotherapy for the reduction of elevated intraocular pressure in patients with chronic glaucoma or ocular hypertension, or as adjunctive therapy in patients not adequately controlled on other agents [6]. Bimatoprost selectively mimics the effects of a naturally occurring substance, prostamide [6].

The New Zealand data sheet for bimatoprost states that bimatoprost and prostamides differ from prostaglandins in the following ways [6]:

- prostamides are biosynthesized from a different precursor, anandamide
- bimatoprost does not stimulate any previously described prostanoid receptor
- it is not mitogenic
- it does not contract the human uterus
- it is electrochemically neutral.

Bimatoprost is also available in combination with timolol. The combined effects of these two components achieve greater intraocular pressure reduction from their complementary mechanisms of action [7]. Ganfort (bimatoprost and timolol) is indicated for the reduction of intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension who are insufficiently responsive to monotherapy.

Timolol is a non-selective β_1 and β_2 -adrenergic receptor blocking agent [8]. Timolol is thought to lower intraocular pressure by decreasing the formation of aqueous humour but the exact mechanism of action is not known [8].

2.1.2 Latanoprost

Latanoprost is a selective prostaglandin F₂ α analogue [9]. It is a selective prostanoid FP receptor agonist which reduces the intraocular pressure by increasing the outflow of aqueous humour [9].

Latanoprost eye drop solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension [9].

Latanoprost is also available in combination with timolol to achieve additional intraocular pressure reduction as these two components decrease elevated intraocular pressure by different mechanisms of action [10]. The combination medicine is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are insufficiently responsive to beta-blockers, prostaglandins or other intraocular pressure lowering medications [10]. The combination product should not be used to initiate therapy [10].

2.1.3 Travoprost

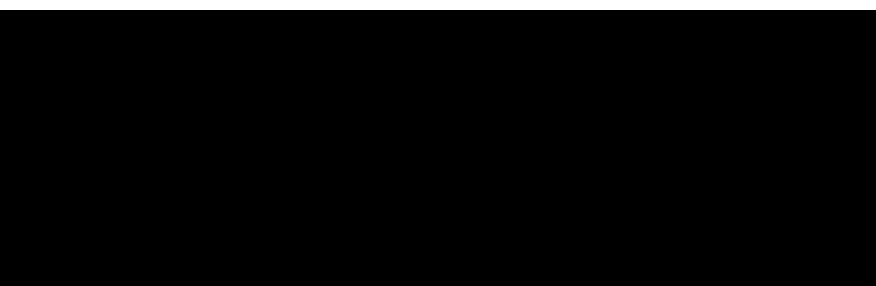
Travoprost is a prostaglandin F₂ analogue and is a highly selective full agonist with high affinity for the prostaglandin FP receptor [11]. As with bimatoprost and latanoprost, this medicine reduces intraocular pressure by increasing the outflow of aqueous humour [11]. Travoprost eye drops are indicated in adults to decrease elevated intraocular pressure in ocular hypertension and open-angle glaucoma. Travoprost eye drops may be used as first line monotherapy or as adjunctive therapy [11].

Travoprost is also available as a combination product with timolol.

2.2 Prostaglandin associated periorbitopathy

PAP was first described in 2004 and since then there have been many case reports and studies looking at PAP [4].

The term prostaglandin-associated periorbitopathy was first invented by Dr Stanley Berke in 2012 and has been described in a number of different ways. Sakata et al state PAP is now well recognised as a group of clinical and cosmetic changes in any one of up to ten factors [12], which are presented in Table 1.



Patradul et al state that PAP is a group of clinical findings that consists of an absence of dermatochalasis (excess of skin in the upper or lower eyelid), a deep crease in the upper eyelid, ptosis (drooping) of the upper eyelid, decreased prominence of the inferior orbital fat pads, enophthalmos (the eyeball moves backward in the eye socket), orbital fat atrophy, flattening of the lower eyelid bags, inferior scleral show (the white sclera can be seen below the iris), tight orbits and deepening of the upper eyelid sulcus (DUES) [13]. Patradul et al

mention that PAP can affect patient care in many ways including difficulty in intraocular pressure measurement, difficulty during surgery and cosmetic concerns [13].

The United Kingdom Summary of medicinal Product Characteristics (SmPC) for Lumigan describes PAP as the following in section 4.8 [14]:

“Prostaglandin analogues including LUMIGAN can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with LUMIGAN, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.”

While changes are typically mild, the possible side effects from treatment may not be insignificant for the person being treated. The New Zealand data sheet for bimatoprost mentions that some eye changes may be permanent and lead to differences in appearance between the eyes when only one eye is treated [6]:

“Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated. Periorbital tissue pigmentation has been reported to be reversible in some patients.”

Fong et al reported on a single person case report concerning a 72 year old woman who presented with a 1 year history of audible clicking sounds when blinking (see section 3.1.18.3) [15]. The authors named this ‘blepharothorevia’ and consider it to be added to the growing list of features of PAP.

DUES is a side effect of prostaglandin analogue treatment. A literature search by Di Staso et al (see section 3.1.6) reports the prevalence of DUES to be 44% after at least three months of therapy. The incidence ranges from 25 to 60% and is noted to be significantly higher in patients treated with bimatoprost (60%) than with latanoprost (6%) and travoprost (53%) [16]. The authors also found that DUES-related symptoms reduce or disappear in 85% of patients after switching from bimatoprost to latanoprost [16].

Below is a picture of a patient with DUES. This image has been taken from an article by Patchinsky et al [17].

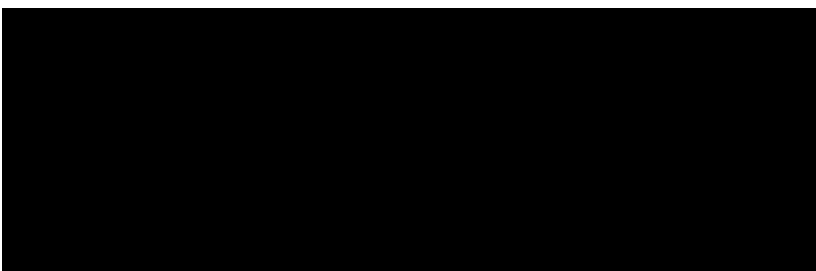


Figure 1 Bilateral PAP with mainly deepening of the upper lid sulcus after five years of timolol/bimatoprost eye drop use [17].

A second figure below shows DUES (top) and the improvement (bottom) once prostaglandin analogue treatment stopped. This image has been taken from an article by Sano et al (section 3.1.2) [18].

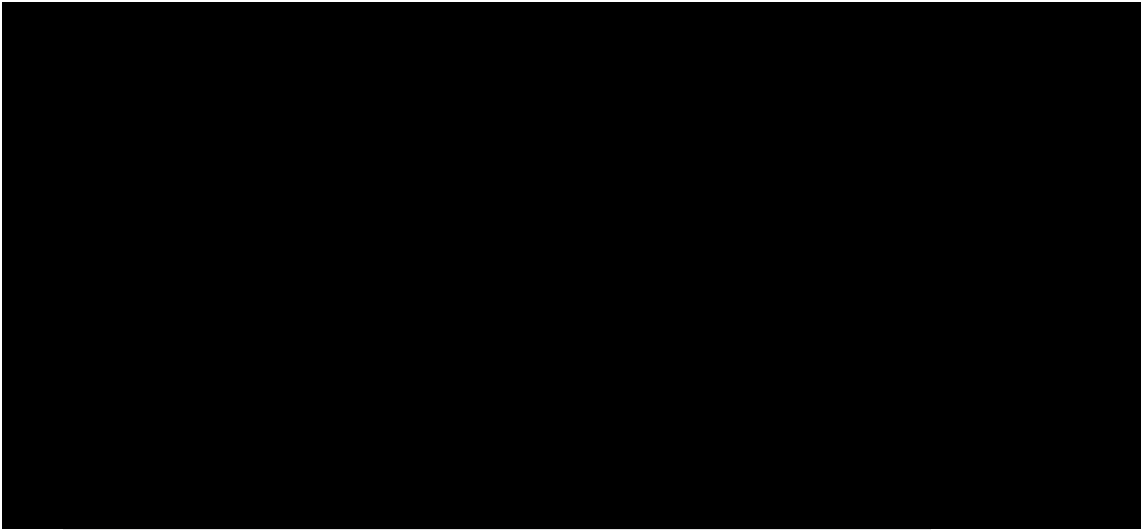


Figure 2 The photograph shows deepening of the upper eyelid sulcus (top). The photograph shows an improvement in deepening of the upper eyelid sulcus (bottom) [18].

Lastly, the effects of unilateral treatment can be seen in the figure below. This image has been taken from an article by Kim et al [19].

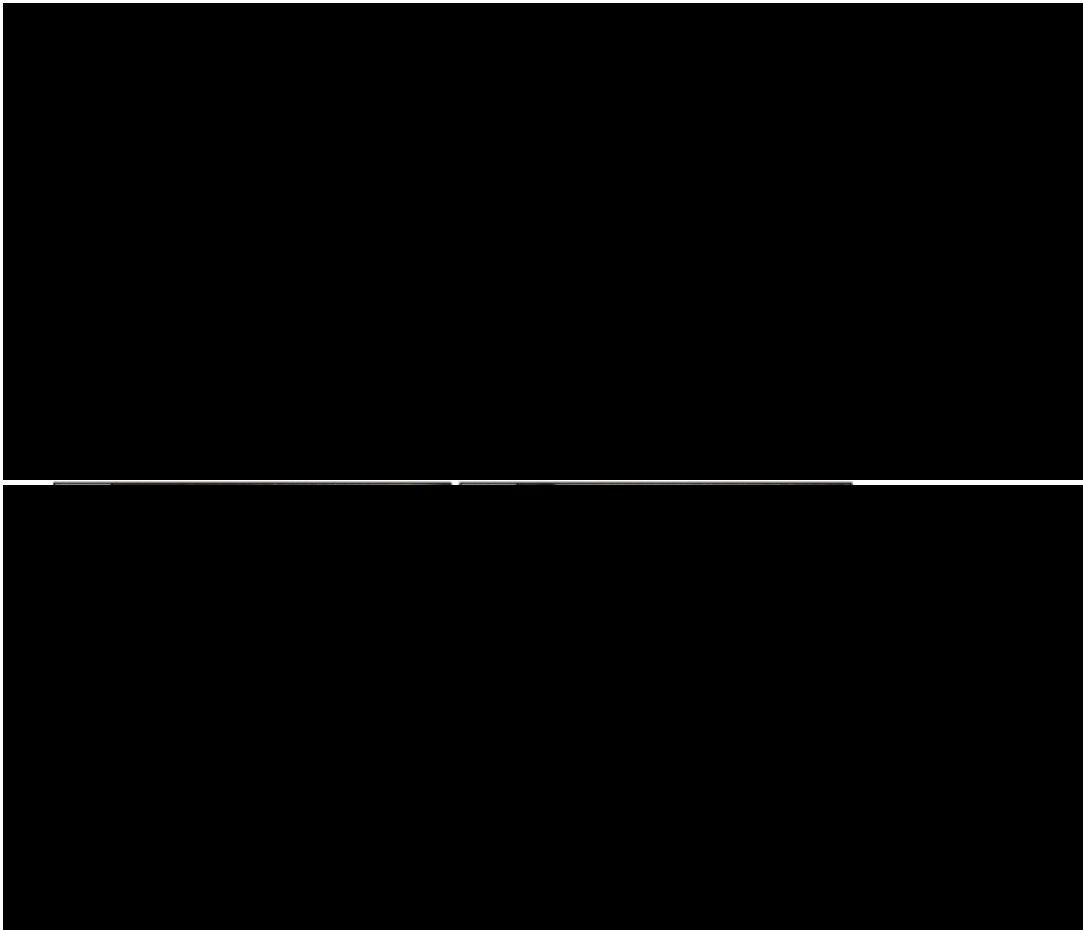


Figure 3 Standardised clinical photographs of a childhood glaucoma patient with long-term unilateral prostaglandin analogue exposure [19].

Most recently, PAP has thought to be caused by orbital fat atrophy from inhibition of adipogenesis (formation of fat cells) through FP receptor stimulation [13]. Sakata et al have illustrated this mechanism (Figure 4) [12]. Prostaglandin analogues (PGAs) bind to the prostaglandin $F_{2\alpha}$ receptor on orbital preadipocytes which activates mitogen-activated protein kinase (MAPK). This results in phosphorylation and inactivation of peroxisome proliferator activated receptor gamma (PPAR γ). This causes an inhibition of adipocyte differentiation, decreases LPL levels and decreases fat accumulation in adipocytes [12].

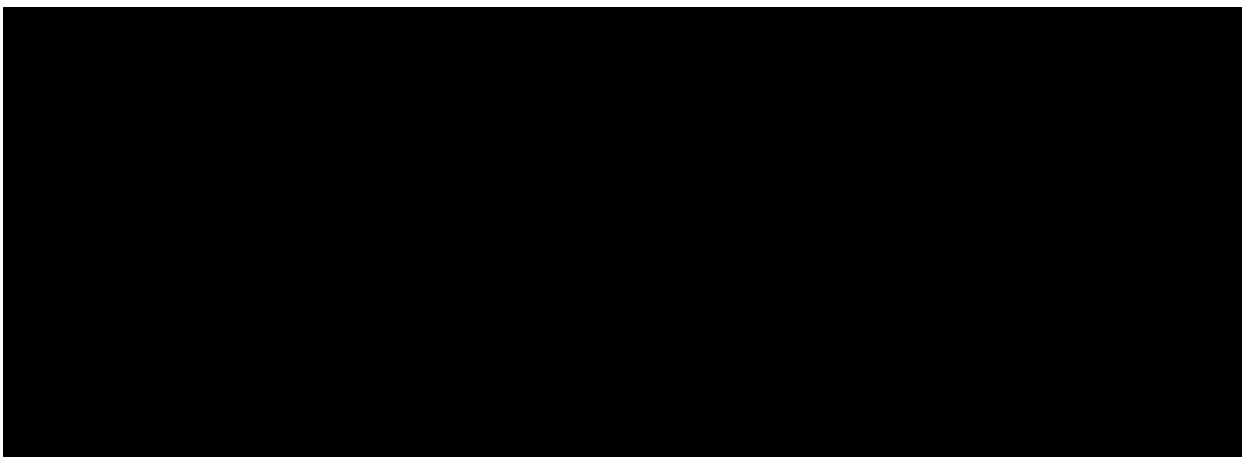


Figure 4 Mechanism of action and impact of PGAs on adipose changes in PAP (Image taken from Sakata et al, 2021 [12])

It has been reported in literature that the occurrence of PAP with prostaglandin analogue use is a significant problem at the same time as prescribing of these medicines by ophthalmologists is increasing [20]. Clinicians

should be aware of the effects of PAP [20]. This is even more important in Caucasian eyes and unilateral administration where a deep upper eyelid sulcus is more obvious [20].

2.3 Data sheets

2.3.1 New Zealand

The information in Table 2 below is related to eye disorders and has been taken from data sheets published on the Medsafe website at 21 March 2022. Products listed in the table are those that have a regulatory status of consent given.

Using the information on PAP presented in section 2.2, terms considered to be related to PAP are shown in bold.

Table 2 Information regarding eye disorders in New Zealand data sheets for available products

Product (sponsor)	Section 4.4 (warnings and precautions)	Section 4.8 (adverse events)
Bimatoprost		
Bimatoprost Multichem Eye drops, solution, 0.3 mg/mL (Multichem)	During treatment with bimatoprost eye drops, darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward ocular effects have been observed. Increased iris pigmentation has also been reported. Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation . Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated. Periorbital tissue pigmentation has been reported to be reversible in some patients.	<u>Clinical trials</u> Very common (>10%): conjunctival hyperaemia, growth of eyelashes , ocular pruritus. Common (<10%): allergic conjunctivitis, asthenopia, blepharitis, blepheral pigmentation, conjunctival oedema, corneal erosion, eye discharge, eyelash darkening , eyelid erythema, eyelid pruritus, eye pain, foreign body sensation, increased iris pigmentation , lacrimation increased, ocular burning, ocular dryness, ocular irritation, photophobia, pigmentation of periocular skin , superficial punctate keratitis, tearing, visual disturbance/blurred vision and worsening of visual acuity. Uncommon (<1%): blepharospasm, eyelid oedema, eyelid retraction , iritis, retinal haemorrhage. <u>Post-marketing</u> Periorbital and lid changes including deepening of the eyelid sulcus , erythema (periorbital), macular edema, ocular discomfort.
Latisse Topical solution, 0.3 mg/mL, (Allergan)	Increased pigmentation of periorbital tissue (eyelid), eyelashes and the iris . Post-marketing reports of perceived colour changes of the iris have been received. Macular oedema, including cystoid macular oedema, has been reported.	<u>Clinical trials</u> Common: eye pruritus, conjunctival hyperaemia, eye irritation, erythema of eyelid. <u>Post-marketing</u> Eye disorders: Blepharitis, Deepened lid sulcus (enophthalmos) , dry eye, eye discharge, eye pain, eye

		swelling, eyelid irritation, eyelid oedema, eyelid pain, eyelids pruritus, iris hyperpigmentation , lacrimation increased, foreign body sensation, dry skin of the eyelid and/or periocular area and vision blurred.
Lumigan Eye drops, solution, 0.3 mg/mL (Allergen)	During treatment with bimatoprost, darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward ocular effects have been observed. Increased iris pigmentation has also been reported. Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated. Periorbital tissue pigmentation has been reported to be reversible in some patients.	<p><u>Clinical trials</u></p> <p>In the two pivotal monotherapy trials (715 patients), the most frequently reported treatment-related adverse events were: conjunctival hyperaemia in up to 42%, growth of eyelashes in up to 36% and ocular pruritus in up to 14% of patients. The incidence of conjunctival hyperaemia at baseline was 25.1% and 17.8% in patients allocated to treatment with LUMIGAN® eye drops once daily and timolol twice daily, respectively.</p> <p>Very common (>10%): conjunctival hyperaemia, growth of eyelashes, ocular pruritus. Common (<10%): allergic conjunctivitis, asthenopia, blepharitis, blepheral pigmentation, conjunctival oedema, corneal erosion, eye discharge, eyelash darkening, eyelid erythema, eyelid pruritus, eye pain, foreign body sensation, increased iris pigmentation, lacrimation increased, ocular burning, ocular dryness, ocular irritation, photophobia, pigmentation of periocular skin, superficial punctate keratitis, tearing, visual disturbance/blurred vision and worsening of visual acuity. Uncommon (<1%): blepharospasm, eyelid oedema, eyelid retraction, iritis, retinal haemorrhage.</p> <p><u>Post-marketing</u></p> <p>Periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos and eyelid retraction; erythema (periorbital), eyelid oedema, macular oedema, ocular discomfort.</p>
Lumigan PF Eye drops, solution, 0.3 mg/mL (Allergen)	During treatment with bimatoprost, darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no	<p><u>Clinical trials</u></p> <p>Very common (>10%): conjunctival hyperemia, growth of eyelashes, ocular pruritus.</p>

	<p>consequent untoward ocular effects have been observed. Increased iris pigmentation has also been reported. Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated. Periorbital tissue pigmentation has been reported to be reversible in some patients.</p>	<p>Common ($\geq 1\%$ to $<10\%$): allergic conjunctivitis, asthenopia, blepharitis, conjunctival oedema, corneal erosion, eye discharge, eyelash darkening, eyelid erythema, eyelid pruritus, eye pain, foreign body sensation, increased iris pigmentation, ocular burning, ocular dryness, ocular irritation, photophobia, pigmentation of periocular skin, superficial punctate keratitis, tearing, visual disturbance and worsening of visual acuity.</p> <p>Uncommon ($<1\%$): blepharospasm, eyelid oedema, eyelid retraction, iritis, retinal hemorrhage.</p> <p>Unknown: deepened lid sulcus (enophthalmos), erythema (periorbital), eyelid edema, macular edema.</p> <p><u>Post-marketing</u></p> <p>Eye discharge, ocular discomfort, Periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos and eyelid retraction.</p>
Bimatoprost/ timolol		
<p>Ganfort PF 0.3/5 Eye drops, solution, 300mcg/mL & 5mg/mL (Allergen)</p>	<p>Cystoid macular oedema has been reported with GANFORT®. Darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward ocular effects were observed. Periorbital tissue pigmentation has been reported to be reversible in some patients. Increased iris pigmentation was also reported. Before treatment is initiated, patients should be informed of the possibility of eyelash growth, and periorbital skin hyperpigmentation and increased iris pigmentation since these have been observed during treatment with GANFORT® PF 0.3/5. Some of these changes may be permanent and may lead to differences in appearance between the eyes if only one eye is treated. There is the potential for hair growth to occur in areas where</p>	<p><u>Clinical trials</u></p> <p>Undesirable effects considered related to treatment that were reported in $\geq 1\%$ of patients during treatment with GANFORT® PF 0.3/5. Most were ocular, mild and none were serious.</p> <p>Conjunctival hyperemia 21.2%, Eye pruritus 4.3% Dry eye 3.2% Punctate keratitis 2.9% Eye pain 2.5% Foreign body sensation in eyes 2.2% Eye irritation 2.2% Growth of eyelashes 1.4% Lacrimation increased 1.4% Conjunctival irritation 1.4% Photophobia 1.1% Erythema of eyelid 1.1%.</p> <p><u>Post-marketing</u></p> <p>Eye swelling, Ocular discomfort. Corneal erosion, burning sensation, eye discharge, visual disturbance, eyelid pruritus, iris hyperpigmentation, deepening of eyelid sulcus, cystoid macular oedema.</p>

	GANFORT® PF 0.3/5 solution comes repeatedly in contact with the skin surface.	Additional adverse reactions reported with one of the components (bimatoprost): Allergic conjunctivitis, conjunctival oedema, erythema (periorbital), eyelash darkening , hair growth abnormal, vision blurred, blepharospasm, retinal haemorrhage, asthenopia, blepharitis, iritis, eyelid oedema, visual acuity worsened, eye discharge, periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos and eyelid retraction.
Ganfort® 0.3/5 Eye drops, solution (Allergen)	See above.	<p><u>Clinical trials</u></p> <p>The most common adverse events in the bimatoprost group were conjunctival hyperaemia (approximately 43% of patients), eye pruritus (approximately 9% of patients) and blepharal pigmentation (approximately 9% of patients). Very Common (>1/10): conjunctival hyperaemia, growth of eyelashes Common (>1/100, <1/10): burning sensation, eye pruritus, superficial punctate keratitis, eye dryness, foreign body sensation, stinging sensation in the eye, eyelid erythema, photophobia, eye pain, eye discharge, eyelid pruritus, visual disturbance, corneal erosion Uncommon (>1/1000, <1/100): eye irritation, blepharitis, epiphora, iritis, eyelid oedema, eyelid pain, conjunctival oedema, asthenopia, trichiasis, visual acuity worsened.</p> <p><u>Post-marketing</u></p> <p>Cystoid macular oedema, eye swelling, lid sulcus deepened (enophthalmos), iris hyperpigmentation, vision blurred, ocular discomfort.</p> <p>Additional adverse reactions that have been seen with one of the components (bimatoprost) Ocular pruritus, allergic conjunctivitis, eyelash darkening, ocular burning, ocular dryness, ocular irritation, pigmentation of periocular skin, tearing, blepharospasm,</p>

		retinal haemorrhage, eye discharge; periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos and eyelid retraction.
Latanoprost		
Latanoprost Eye drops, solution, 50 mcg/mL (Teva)	Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Eyelid skin darkening , which may be reversible. Latanoprost may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation and number of lashes or hairs, and misdirected growth of eyelashes.	<p><u>Clinical trials</u> Adverse events reported in three pivotal trials – blurred vision, burning, conjunctivitis, excessive tearing, eye pain, foreign body sensation, hyperaemia, iris hyperpigmentation, itching, punctate epithelial erosions. Most of the adverse events reported for latanoprost relate to the ocular system.</p> <p>Very common: Iris hyperpigmentation; eye irritation (burning, grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (increased length, thickness, pigmentation and number of eyelashes). Common: Mild to moderate ocular hyperaemia; punctate keratitis (mostly without symptoms); blepharitis; eye pain; conjunctivitis; vision blurred; eyelid oedema, localised skin reaction on the eyelids. Uncommon: Iritis, uveitis; keratitis; macular oedema including cystoid macular oedema; photophobia. Rare: Corneal oedema; corneal erosion; periorbital oedema; darkening of the palpebral skin of the eyelids; periorbital and lid changes resulting in deepening of the eyelid sulcus; trichiasis.</p> <p><u>Post-marketing</u> Pseudopemphigoid of ocular conjunctiva, iris cyst.</p>
Latanoprost/ timolol		
Arrow - Lattim Eye drops, solution, 0.05mg/mL, 5mg/mL (Teva)	Ocular effects - Latanoprost may gradually change eye colour by increasing the amount of brown pigment in the iris. Eyelid and eyelash changes - Eyelid skin darkening , which may be reversible, has been reported. Latanoprost may	For latanoprost, the majority of adverse reactions relate to the ocular system. <u>Clinical trials</u> Very common: Iris hyperpigmentation . Common: Eye pain, eye irritation (including stinging, burning, itching, foreign

	<p>gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, and number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.</p> <p>Macular oedema - Macular oedema, including cystoid macular oedema, has been reported.</p>	<p>body sensation). Uncommon: Corneal disorders, conjunctivitis, blepharitis, eye hyperaemia, vision blurred, lacrimation increased.</p> <p><u>Clinical/post-marketing/literature</u></p> <p>Additional adverse reactions have been reported specifically for latanoprost: Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes); punctate keratitis, periorbital oedema; iritis; uveitis; macular oedema including cystoid macular oedema dry eye; keratitis; corneal oedema; corneal erosion; trichiasis; iris cyst; photophobia; periorbital and lid changes resulting in deepening of the eyelid sulcus; eyelid oedema; localised skin reaction on the eyelids; pseudopemphigoid of the ocular conjunctiva+; darkening of the palpebral skin.</p> <p>+ may be potentially related to the preservative benzalkonium chloride.</p>
<p>Travoprost</p> <p>Travatan Eye drops, solution, 0.004 %, PQ Eye Drops (Novartis)</p>	<p>Travatan Eye Drops may gradually change the eye colour. Unilateral treatment can result in permanent heterochromia. Periorbital and/or eyelid skin darkening has been reported. Periorbital and lid changes including deepening of the eyelid sulcus have been observed with prostaglandin analogues. Travatan Eye Drops may gradually change eyelashes in the treated eye(s); these changes include: increased length, thickness, pigmentation, and/or number of lashes. Macular oedema has been reported.</p>	<p>The most frequently reported treatment-related undesirable effect with Travatan Eye Drops monotherapy was hyperaemia of the eye (21.8%), which included ocular, conjunctival, or scleral hyperaemia.</p> <p><u>Clinical trials</u></p> <p>Very common: conjunctival hyperaemia, ocular hyperaemia, iris hyperpigmentation.</p> <p>Common: punctate keratitis, anterior chamber cell, anterior chamber flare, eye pain, photophobia, eye discharge, ocular discomfort, eye irritation, abnormal sensation in eye, foreign body sensation in eyes, visual acuity reduced, vision blurred, dry eye, eye pruritus, lacrimation increased, erythaema of eyelid, eyelid oedema, eyelids pruritis, growth of eyelashes, eyelash discolouration.</p> <p>Uncommon: corneal erosion, iridocyclitis, iritis, uveitis, keratitis, anterior chamber inflammation, eye swelling,</p>

		<p>corneal staining, photopsia, blepharitis, conjunctival oedema, halo vision, conjunctivitis allergic, conjunctival disorder, conjunctivitis, conjunctival follicles, hypoaesthesia eye, ectropion, keratoconjunctivitis sicca, cataract, eye allergy, eyelid pain, eyelid disorder, eyelid margin crusting, scleral hyperaemia, asthenopia.</p> <p><u>Class Effects</u></p> <p>As with other prostaglandin analogues, Travatan Eye Drops may gradually change eyelashes in the treated eye(s); these changes were observed in about half of patients in clinical trials and include: increased length, thickness, pigmentation, and/or number of lashes. However, fewer than 1% reported these as adverse events. The mechanism of eyelash changes and their long-term consequences are currently unknown.</p> <p><u>Post-marketing</u></p> <p>Very Common: ocular hyperaemia.</p> <p>Common: eye pain, eye pruritus, dry eye, eye irritation, iris hyperpigmentation, ocular discomfort.</p> <p>Uncommon: corneal erosion, punctate keratitis, keratitis, iritis, cataract, visual acuity reduced, conjunctivitis, anterior chamber inflammation, blepharitis, vision blurred, photophobia, periorbital oedema, eyelids pruritus, eye discharge, eyelid margin crusting, lacrimation increased, erythema of eyelid, growth of eyelashes.</p> <p>Rare: uveitis, iridocyclitis, ophthalmic herpes simplex, conjunctival follicles, conjunctival oedema, hypoaesthesia eye, eye inflammation, trichiasis, eczema eyelids, anterior chamber pigmentation, asthenopia, eye allergy, eyelid irritation, eyelash hyperpigmentation, eyelash thickening.</p> <p>Frequency not known: Eye disorders: macular oedema, lid sulcus deepened.</p>
Travoprost/ timolol		

<p>DuoTrav Eye drops, solution, 40 micrograms/mL, 5 mg/mL (Novartis)</p>	<p>Travoprost may gradually change the eye colour. Unilateral treatment can result in permanent heterochromia. Periorbital and/or eyelid skin darkening and deepening of the eyelid sulcus have been reported in association with the use of Travoprost. Eyelash changes occurred in over a third of patients treated with DuoTrav Eye Drops. These changes include: increased length, thickness, pigmentation, and/or number of lashes. Although not reported during pivotal clinical trials with DuoTrav Eye Drops, macular oedema, including cystoid macular oedema, has been reported during treatment with prostaglandin F2α analogues. Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.</p>	<p><u>Clinical trials</u> Common: eye pain, ocular discomfort, dry eye, eye pruritus, ocular hyperaemia Uncommon: punctate keratitis, iritis, photophobia, vision blurred, conjunctivitis, meibomianitis, eyelid margin crusting, asthenopia, lacrimation increased, growth of eye lashes. Additional adverse reactions seen for travoprost: Uveitis, conjunctival disorder, conjunctival follicles, iris hyperpigmentation. <u>Post-marketing</u> Common: eye pain, dry eye, eye pruritus, ocular discomfort, ocular hyperaemia. Uncommon: punctate keratitis, iritis, conjunctivitis, vision blurred, photophobia, eyelids pruritus, asthenopia, meibominitis, eyelid margin crusting, growth of eyelashes. Frequency not known Macular oedema, keratitis, blepharitis, conjunctivitis, erythema of eyelid, eye swelling, lacrimation increased, eyelid oedema, eyelid ptosis, eye irritation. DuoTrav (BAK-preserved) – clinical Very common: ocular discomfort, ocular hyperaemia. Common: punctate keratitis, anterior chamber inflammation, eye pain, photophobia, eye swelling, conjunctival haemorrhage, visual acuity reduced, visual disturbance, vision blurred, dry eye, eye pruritus, conjunctivitis, lacrimation increased, erythema of eyelid, blepharitis, asthenopia, growth of eyelashes. Uncommon: corneal erosion, keratitis, eye allergy, conjunctival oedema, eyelid oedema. Rare: iritis. Not known; macular oedema, eyelid ptosis, corneal disorder <u>DuoTrav (BAK-preserved) – post-marketing</u></p>
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		<p>Very common: ocular hyperaemia. Common: punctate keratitis, vision blurred, dry eye, eye pain, eye pruritus, ocular discomfort, eye irritation. Uncommon: keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, conjunctival haemorrhage, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes Rare: corneal erosion, trichiasis, distichiasis. Frequency not known: Macular oedema <u>Adverse reactions reported during clinical studies with DuoTrav</u> Very common: ocular hyperaemia. Common: punctate keratitis, vision blurred, dry eye, eye pain, eye pruritus, ocular discomfort, eye irritation. Uncommon: keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes. Rare: corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis. <u>Adverse reactions from spontaneous reports and literature cases</u> Macular oedema, eyelid ptosis, lid sulcus deepened, iris hyperpigmentation.</p>
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Comment:

A number of eye disorders, including clinical characteristics of PAP, are listed in section 4.4 and section 4.8 of New Zealand data sheets for prostaglandin analogues (bimatoprost, latanoprost and travoprost). PAP is not specifically stated in any data sheet.

2.3.2 Australia

Table 3 below includes a selection of product information from Australia for comparison.

Table 3 Information regarding eye disorders in a selection of Australian product information

Product (sponsor)	Section 4.4 (warnings and precautions)	Section 4.8 (adverse events)
<p>Bimatoprost</p> <p>Lumigan bimatoprost 300 mcg/ml eye drops bottle (Allergen)</p>	<p>Darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening). Increased iris pigmentation has also been reported. Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin and increased iris pigmentation. Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated. Periorbital tissue pigmentation has been reported to be reversible in some patients. There is the potential for hair growth to occur in areas where LUMIGAN solution comes repeatedly in contact with the skin surface. Macular oedema, including cystoid macular oedema, has been reported.</p>	<p>In the two pivotal monotherapy trials (715 patients) the most frequently reported treatment related adverse events were: conjunctival hyperemia in up to 42%, growth of eyelashes in up to 36% and ocular pruritus in up to 14% of patients.</p> <p><u>Clinical trials</u> Very common (>10%): conjunctival hyperemia, growth of eyelashes, ocular pruritus Common (<10%): allergic conjunctivitis, asthenopia, blepharitis, blepheral pigmentation, conjunctival oedema, corneal erosion, eye discharge, eyelash darkening, eyelid erythema, eyelid pruritus, eye pain, foreign body sensation, increased iris pigmentation, lacrimation increased, ocular burning, ocular dryness, ocular irritation, photophobia, pigmentation of periocular skin, superficial punctate keratitis, tearing, visual disturbance/blurred vision and worsening of visual acuity Uncommon (<1%): blepharospasm, eyelid oedema, eyelid retraction, iritis, retinal hemorrhage</p> <p><u>Post-marketing</u> Periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos and eyelid retraction; erythema (periorbital), eyelid oedema, macular oedema, ocular discomfort.</p>
<p>Bimatoprost; timolol</p> <p>VIZO-PF BIMATOTIM 0.3/5 (AFT Pharmaceuticals)</p>	<p>Cystoid macular oedema has been reported with Bimatoprost/Timolol. Darkening of the eyelid skin and gradual increased eyelash growth (lengthening, darkening and thickening) with no consequent untoward</p>	<p><u>Clinical trials</u> Conjunctival hyperemia 21.2% Eye pruritus 4.3% Dry eye 3.2%</p>

	<p>ocular effects observed. Periorbital tissue pigmentation has been reported. Increased iris pigmentation was also reported. Before treatment is initiated, patients should be informed of the possibility of eyelash growth, and periorbital skin hyperpigmentation and increased iris pigmentation, since these have been observed during treatment with bimatoprost and Bimatoprost/Timolol. There is the potential for hair growth to occur in areas where Bimatoprost/Timolol (preservative free) eye drops solution comes repeatedly in contact with the skin surface.</p>	<p>Punctate keratitis 2.9% Eye pain 2.5% Foreign body sensation in eyes 2.2% Eye irritation 2.2% Growth of eyelashes 1.4% Lacrimation increased 1.4% Conjunctival irritation 1.4% Photophobia 1.1% Erythema of eyelid 1.1% <u>Post-marketing</u> Eye swelling, ocular discomfort. Corneal erosion, burning sensation, eye discharge, visual disturbance, eyelid pruritus, iris hyperpigmentation, deepening of eyelid sulcus, cystoid macular oedema. Adverse reactions that have been seen with bimatoprost may also occur with this combination medicine - Allergic conjunctivitis, conjunctival oedema, erythema (periorbital), eyelash darkening, hair growth abnormal, vision blurred, blepharospasm, eyelid retraction, retinal haemorrhage, asthenopia, blepharitis, iritis, eyelid oedema, visual acuity worsened.</p>
Latanoprost		
<p>XALATAN Latanoprost 50 microgram/mL eye drops bottle (Aspen Pharmacare)</p>	<p>Iris Pigmentation Changes: XALATAN may gradually change eye colour. Before treatment is instituted, patients should be informed of the possibility of a permanent change in eye colour. Eyelid and Eyelash Changes Eyelid skin darkening, which may be reversible, has been reported in association with the use of XALATAN. XALATAN may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation and number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.</p>	<p><u>Clinical trials</u> Blurred vision, burning, conjunctivitis, excessive tearing, eye pain, foreign body sensation, hyperaemia, iris pigmentation, itching, punctate epithelial erosions. Very common (>10% patients) Iris hyperpigmentation; eye irritation (burning, grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes (increased length, thickness, pigmentation and number of eyelashes). Common (1 –10% patients) Mild to moderate ocular hyperaemia; punctate keratitis (mostly without symptoms); blepharitis; eye pain;</p>

		<p>conjunctivitis; vision blurred; eyelid oedema, localised skin reaction on the eyelids. Uncommon (< 1% patients) Iritis, uveitis; keratitis; macular oedema including cystoid macular oedema; photophobia Rare (< 0.1% patients) Corneal oedema; corneal erosion; periorbital oedema; darkening of the palpebral skin of the eyelids; periorbital and lid changes resulting in deepening of the eyelid sulcus; trichiasis. <u>Post-marketing</u> Pseudopemphigoid of ocular conjunctiva, iris cyst.</p>
Latanoprost; timolol		
<p>XALACOM latanoprost 50 microgram/mL, timolol (as maleate) 5 mg/mL eye drops (Aspen Pharmacare)</p>	<p>Iris pigmentation changes - Latanoprost may gradually change the eye colour. Before treatment is instituted patients should be informed of the possibility of a change in eye colour. Unilateral treatment can result in permanent heterochromia. Eyelid and eyelash changes - Eyelid skin darkening, which may be reversible, has been reported in association with the use of latanoprost. Latanoprost may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, and number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.</p>	<p><u>Clinical trials</u> Blepharitis, cataract, conjunctival disorder, conjunctivitis, corneal disorder, corneal ulceration, cystoid macular edema, epiphora, errors of refraction, eye hyperaemia, eye pain, increased intraocular pressure, iris hyperpigmentation, iritis, irritation eye, keratitis, oedema eyelid, photophobia, retinal disorder, uveitis, vision abnormal, optic atrophy. Adverse events reported for single component latanoprost: Eye irritation (burning, grittiness, itching, stinging, tearing, redness and foreign body sensation), punctate keratitis, macular oedema, corneal oedema, corneal erosions, eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes), trichiasis, blurred vision, periorbital and lid changes resulting in deepening of the eyelid sulcus, darkening of the palpebral skin of the eyelids, localised skin reaction on the eyelids. <u>Post-marketing</u> Iris cyst, pseudopemphigoid of the ocular conjunctiva.</p>
Travoprost		

<p>TRAVATAN 0.004% travoprost 40 microgram/mL eye drop solution bottle (Novartis)</p>	<p>TRAVATAN Eye Drops may gradually change the eye colour. Before treatment is instituted patients must be informed of the possibility of these changes. Unilateral treatment can result in permanent heterochromia. Periorbital and/or eyelid skin darkening has been reported. Periorbital and lid changes including deepening of the eyelid sulcus have been observed with prostaglandin analogues. TRAVATAN Eye Drops may gradually change eyelashes in the treated eye(s); these changes include: increased length, thickness, pigmentation, and/or number of lashes.</p>	<p><u>Clinical trials</u></p> <p>Very common: conjunctival hyperaemia, ocular hyperaemia, iris hyperpigmentation</p> <p>Common: punctate keratitis, anterior chamber cell, anterior chamber flare, eye pain, photophobia, eye discharge, ocular discomfort, eye irritation, abnormal sensation in eye, foreign body sensation in eyes, visual acuity reduced, vision blurred, dry eye, eye pruritus, lacrimation increased, erythaema of eyelid, eyelid oedema, eyelids pruritis, growth of eyelashes, eyelash discolouration.</p> <p>Uncommon: corneal erosion, iridocyclitis, iritis, uveitis, keratitis, anterior chamber inflammation, eye swelling, corneal staining, photopsia, blepharitis, conjunctival oedema, halo vision, conjunctivitis allergic, conjunctival disorder, conjunctivitis, conjunctival follicles, hypoaesthesia eye, ectropion, keratoconjunctivitis sicca, cataract, eye allergy, eyelid pain, eyelid disorder, eyelid margin crusting, scleral hyperaemia, asthenopia.</p> <p>Class effects: As with other prostaglandin analogues, TRAVATAN Eye Drops may gradually change eyelashes in the treated eye(s); these changes were observed in about half of patients in clinical trials and include: increased length, thickness, pigmentation, and/or number of lashes. However, fewer than 1% reported these as adverse events. The mechanism of eyelash changes and their long-term consequences are currently unknown.</p> <p>Additional ADRs identified from long-term clinical study (frequency uncommon): Anterior chamber pigmentation; Corneal epithelium defect; Corneal pigmentation; Dark circles under eyes; Dizziness; Drug hypersensitivity; Eye inflammation; Hypercholesterolaemia; Hypertension;</p>
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		<p>Influenza; Keratitis herpetic; Macular degeneration; Meibomianitis; Metrorrhagia; Mydriasis; Pigment dispersion syndrome; Rash.</p> <p><u>Post-marketing</u> Very Common: ocular hyperaemia. Common: eye pain, eye pruritus, dry eye, eye irritation, iris hyperpigmentation, ocular discomfort. Uncommon: corneal erosion, punctate keratitis, keratitis, iritis, cataract, visual acuity reduced, conjunctivitis, anterior chamber inflammation, blepharitis, vision blurred, photophobia, periorbital oedema, eyelids pruritus, eye discharge, eyelid margin crusting, lacrimation increased, erythema of eyelid, growth of eyelashes. Rare: uveitis, iridocyclitis, ophthalmic herpes simplex, conjunctival follicles, conjunctival oedema, hypoaesthesia eye, eye inflammation, trichiasis, eczema eyelids, anterior chamber pigmentation, asthenopia, eye allergy, eyelid irritation, eyelash hyperpigmentation, eyelash thickening. Frequency not known: Macular oedema, lid sulcus deepened.</p>
Travoprost; timolol		
<p>DUOTRAV travoprost 0.004% and timolol 0.5% (as maleate) eye drop solution bottle (Novartis)</p>	<p>Travoprost may gradually change the eye colour. Before treatment is instituted patients must be informed of the possibility of these changes. Unilateral treatment can result in permanent heterochromia. Periorbital and/or eyelid skin darkening and deepening of the eyelid sulcus have been reported. Eyelash changes occurred in over a third of patients treated with DuoTrav Eye Drops. These changes include: increased length, thickness, pigmentation, and/or number of lashes.</p>	<p><u>Clinical trials</u> Common: eye pain, ocular discomfort, dry eye, eye pruritus, ocular hyperaemia Uncommon: punctate keratitis, iritis, photophobia, vision blurred, conjunctivitis, meibomianitis, eyelid margin crusting, asthenopia, lacrimation increased, growth of eye lashes. <u>Additional ADRs</u> that have been seen with the single component travoprost: uveitis, conjunctival disorder, conjunctival follicles, iris hyperpigmentation.</p>

		<p><u>DuoTrav (BAK-preserved formulation only):</u> Very common: ocular discomfort, ocular hyperaemia Common: punctate keratitis, anterior chamber inflammation, eye pain, photophobia, eye swelling, conjunctival haemorrhage, visual acuity reduced, visual disturbance, vision blurred, dry eye, eye pruritus, conjunctivitis, eye irritation, lacrimation increased, erythema of eyelid, blepharitis, asthenopia, growth of eyelashes Uncommon: keratitis, iritis, corneal erosion, eye allergy, conjunctival oedema, eyelid oedema. Rare: trichiasis, distichiasis.</p> <p><u>Post-marketing</u> Macular oedema, keratitis, blepharitis, conjunctivitis, erythema of eyelid, eye swelling, lacrimation increased, eyelid oedema, eyelid ptosis, eye irritation, lid sulcus deepened, iris hyperpigmentation.</p> <p><u>DuoTrav (BAK-preserved formulation only):</u> Corneal disorder.</p>
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Comment:

Similarly, to New Zealand data sheets, Australian product information does not specifically state PAP however clinical characteristics are listed as adverse reactions in section 4.8. A large number of eye disorder terms are listed in sections 4.4 and 4.8. Also, like New Zealand data sheets, not all product information are consistent in the listed terms for example ptosis, enophthalmos, eyelid retraction etc are included in some but not all.

2.3.3 United Kingdom

Table 4 below includes a selection of product information from the United Kingdom for comparison.

Table 4 Information regarding eye disorders in a selection of United Kingdom product information

Product (sponsor)	Section 4.4 (warnings and precautions)	Section 4.8 (adverse events)
Bimatoprost		
LUMIGAN 0.3 mg/mL eye drops, solution, in single-dose container (Allergen)	Before treatment is initiated, patients should be informed of the possibility of prostaglandin analogue periorbitopathy (PAP) and increased iris pigmentation , since these have been observed during treatment with LUMIGAN. Some of	Very common - conjunctival hyperaemia, prostaglandin analogue periorbitopathy.

	<p>these changes may be permanent, and may lead to impaired field of vision and differences in appearance between the eyes when only one eye is treated (see section 4.8).</p>	<p>Common - punctate keratitis, eye irritation, foreign body sensation, dry eye, eye pain, eye pruritus, growth of eyelashes, eyelid erythema.</p> <p>Uncommon - asthenopia, conjunctival oedema, photophobia, lacrimation increased, iris hyperpigmentation, blurred vision, eyelid pruritus, eyelid oedema.</p> <p>Not known - eye discharge, ocular discomfort</p> <p><u>Description of selected adverse reactions:</u></p> <p>Prostaglandin analogue periorbitopathy (PAP): Prostaglandin analogues including LUMIGAN can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with LUMIGAN, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.</p> <p>Iris hyperpigmentation: Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more</p>
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		<p>brownish. Neither naevi nor freckles of the iris appear to be affected by the treatment. At 3 months, the incidence of iris hyperpigmentation with bimatoprost 0.3 mg/mL single dose was 0.3%. At 12 months, the incidence of iris pigmentation with bimatoprost 0.3 mg/mL (multi-dose formulation) was 1.5% (see section 4.8) and did not increase following 3 years treatment.</p> <p><u>Additional adverse reactions seen in a clinical study at a higher frequency for multi-dose formulation than single dose formulation:</u></p> <p>Very common - ocular pruritus, growth of eyelashes.</p> <p>Common - asthenopia, conjunctival oedema, photophobia, tearing, increased iris pigmentation; blurred vision.</p> <p><u>Additional adverse reactions seen with the multi-dose formulation:</u></p> <p>Common - corneal erosion, ocular burning, allergic conjunctivitis, blepharitis, worsening of visual acuity, eye discharge, visual disturbance, eyelash darkening.</p> <p>Uncommon - retinal haemorrhage, uveitis, cystoid macular oedema, iritis, blepharospasm, eyelid retraction.</p>
Bimatoprost; timolol		
GANFORT 0.3 mg/ml + 5 mg/ml eye drops, solution (Allergen)	<p>Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid or periocular skin and increased brown iris pigmentation since these have been observed during treatment with bimatoprost and GANFORT. Increased iris pigmentation is likely to be permanent, and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of GANFORT, pigmentation of iris may be permanent. Periorbital tissue pigmentation has been reported to be reversible in some patients.</p>	<p>Very common – conjunctival hyperaemia.</p> <p>Common – punctuate keratitis, corneal erosion, burning sensation, conjunctival irritation, eye pruritus, stinging sensation in the eye, foreign body sensation, dry eye, erythema of eyelid, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus, visual acuity worsened, blepharitis, eyelid oedema, eye irritation, lacrimation increased, growth of eyelashes.</p> <p>Uncommon – iritis, conjunctival oedema, eyelid pain, abnormal sensation in the eye, asthenopia, trichiasis, iris hyperpigmentation, deepening of eyelid sulcus, eyelid retraction, eyelash discolouration (darkening).</p>

		<p>Not known – cystoid macular oedema, eye swelling, vision blurred, ocular discomfort.</p> <p><u>Additional adverse reactions that have been seen with either of the active substances:</u></p> <p>Decreased corneal sensitivity, diplopia, ptosis, choroidal detachment following filtration surgery (see section 4.4), keratitis, blepharospasm, retinal haemorrhage, uveitis.</p>
<p>Bimatoprost/Timolol Aspire 0.3 mg/ml + 5 mg/ml eye drops, solution (Aspire)</p>	<p>Before treatment is initiated, patients should be informed of the possibility of prostaglandin analogue periorbitopathy (PAP) and increased brown iris pigmentation since these have been observed during treatment with bimatoprost and Bimatoprost/Timolol.</p>	<p>Very common – prostaglandin analogue periorbitopathy. Description of selected adverse reactions</p> <p>Prostaglandin analogue periorbitopathy (PAP)</p> <p>Prostaglandin analogues including Bimatoprost/Timolol can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with Bimatoprost/Timolol, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.</p>
Latanoprost		
<p>Xalatan 50 micrograms/mL Eye drops, solution (Upjohn UK Limited)</p>	<p>Xalatan may gradually change eye colour by increasing the amount of brown pigment in the iris. Before treatment is instituted, patients should be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. Reports of macular oedema have occurred. Periorbital skin discolouration has been observed. Latanoprost may gradually change eyelashes and vellus hair in the treated eye and surrounding areas; these changes include increased length, thickness, pigmentation, number of</p>	<p>Very common – Iris hyperpigmentation; mild to moderate conjunctival hyperaemia; eye irritation (burning grittiness, itching, stinging and foreign body sensation); eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation and number of eyelashes).</p> <p>Common – Punctate keratitis, mostly without symptoms; blepharitis; eye pain; photophobia; conjunctivitis</p> <p>Uncommon – Eyelid oedema; dry eye; keratitis; vision blurred; macular oedema including cystoid macular oedema; uveitis.</p>

	<p>lashes or hairs and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.</p>	<p>Rare – Iritis, corneal oedema; corneal erosion; periorbital oedema; trichiasis; distichiasis; iris cyst; localised skin reaction on the eyelids; darkening of the palpebral skin of the eyelids; pseudopemphigoid of ocular conjunctiva Very rare – Periorbital and lid changes resulting in deepening of the eyelid sulcus.</p>
Latanoprost; timolol		
<p>Xalacom 50 micrograms/mL + 5 mg/mL, eye drops, solution (Upjohn UK Limited)</p>	<p>Iris pigmentation changes - Latanoprost may gradually change eye colour. Before treatment is instituted patients should be informed of the possibility of a change in eye colour. Unilateral treatment can result in permanent heterochromia. Eyelid and eyelash changes - Eyelid skin darkening, which may be reversible, has been reported in association with the use of latanoprost. Latanoprost may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, and number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are reversible upon discontinuation of treatment.</p>	<p><u>Xalacom trials</u> Very common – iris hyperpigmentation. Common – Eye pain, eye irritation (including stinging, burning, itching, foreign body sensation). Uncommon - Corneal disorders, conjunctivitis, blepharitis, eye hyperaemia, vision blurred, lacrimation increased. <u>Additional adverse reactions reported for the specific individual components (latanoprost):</u> Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes); punctate keratitis, periorbital oedema; iritis; uveitis; macular oedema including cystoid macular oedema dry eye; keratitis; corneal oedema; corneal erosion; trichiasis; iris cyst; photophobia; periorbital and lid changes resulting in deepening of the eyelid sulcus; eyelid oedema; localised skin reaction on the eyelids; pseudopemphigoid of the ocular conjunctiva; darkening of the palpebral skin.</p>
Travoprost		
<p>TRAVATAN® 40 micrograms/mL eye drops, solution (Novartis)</p>	<p>Eye colour change - TRAVATAN may gradually change the eye colour. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. Periorbital and eye lid changes - In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of TRAVATAN has been reported in 0.4% of patients. Periorbital and lid changes including</p>	<p>Very common – ocular hyperaemia. Common – iris hyperpigmentation, eye pain, ocular discomfort, dry eye, eye pruritus, eye irritation. Uncommon – corneal erosion, uveitis, iritis, anterior chamber inflammation, keratitis, punctate keratitis, photophobia, eye discharge, blepharitis, erythema of eyelid, periorbital oedema, eyelids pruritus, visual acuity reduced, vision blurred, lacrimation increased, conjunctivitis,</p>

	<p>deepening of the eyelid sulcus have also been observed with prostaglandin analogues.</p> <p>TRAVATAN may gradually change eyelashes in the treated eye(s). Changes include: increased length, thickness, pigmentation, and/or number of lashes. The mechanism of eyelash changes and their long-term consequences are currently unknown.</p>	<p>ectropion, cataract, eyelid margin crusting, growth of eyelashes.</p> <p>Rare – iridocyclitis, ophthalmic herpes simplex, eye inflammation, photopsia, eczema eyelids, conjunctival oedema, halo vision, conjunctival follicles, hypoaesthesia eye, trichiasis, meibomianitis, anterior chamber pigmentation, mydriasis, asthenopia, eyelash hyperpigmentation, eyelash thickening.</p> <p>Not known – macular oedema, lid sulcus deepened.</p>
Travoprost; timolol		
DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution (Novartis)	<p>Travoprost may gradually change the eye colour. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia.</p> <p>In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported.</p> <p>Periorbital and lid changes, including deepening of the eyelid sulcus, have been observed with prostaglandin analogues.</p> <p>Travoprost may gradually change eyelashes in the treated eye(s); these changes include: increased length, thickness, pigmentation, and/or number of lashes.</p>	<p>Very common – Ocular hyperaemia</p> <p>Common – Punctate keratitis, eye pain, visual disturbance, vision blurred, dry eye, eye pruritus, ocular discomfort, eye irritation.</p> <p>Uncommon – Keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes, eye allergy, conjunctival oedema, eyelid oedema</p> <p>Rare – Corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis</p> <p>Not known – Macular oedema, eyelid ptosis, lid sulcus deepened, iris hyperpigmentation, corneal disorder</p> <p><u>Additional reactions that have been seen with one of the active substances (travoprost):</u></p> <p>Uveitis, conjunctival follicles, eye discharge, periorbital oedema, eyelids pruritus, ectropion, cataract, iridocyclitis, ophthalmic herpes simplex, eye inflammation, photopsia, eczema eyelids, halo vision, hypoaesthesia eye, anterior chamber pigmentation, mydriasis, eyelash hyperpigmentation, eyelash thickening, visual field defect.</p>

Comment:

The UK SPC for bimatoprost specifically lists PAP in sections 4.4 and 4.8. PAP is not listed consistently in the bimatoprost/timolol combination products. Where PAP is not listed, clinical characteristics are. The reason for the differences between some UK SPCs for products containing bimatoprost is unknown. It could be that they are in the process of being updated.

The remaining SPCs reviewed for latanoprost and travoprost are similar to the New Zealand and Australian product information as they also list clinical characteristics of PAP but no description of PAP specifically.

2.4 Review of bimatoprost and prostaglandin analogue periorbitopathy by the United Kingdom's Committee for medicinal products for human use

The Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the benefit-risk balance of Lumigan (bimatoprost) and requested the MAH should provide a cumulative review on PAP-related adverse events with bimatoprost treatment. [The Committee for medicinal products for human use \(CHMP\) considered the PRAC recommendation and agreed with the PRAC's scientific conclusions.](#)

The PRAC considered a causal relationship between bimatoprost and prostaglandin analogue periorbitopathy to be established based on the available data from literature and spontaneous reports including positive de-challenge in some cases and a plausible mechanism of action.

The CHMP recommended the following variations to the marketing authorisations for bimatoprost containing products:

- Section 4.4

A warning should be amended as follows:

Ocular

~~Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid skin~~ **prostaglandin analogue periorbitopathy (PAP)** and increased iris pigmentation, since these have been observed during treatment with LUMIGAN. Some of these changes may be permanent, and may lead to **impaired field of vision and** differences in appearance between the eyes when only one eye is treated **(see section 4.8).**

~~Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish. Neither naevi nor freckles of the iris appear to be affected by the treatment. At 12 months, the incidence of iris hyperpigmentation with bimatoprost 0.1 mg/ml eye drops, solution was 0.5%. At 12 months, the incidence with bimatoprost 0.3 mg/ml eye drops, solution was 1.5% (see section 4.8 Table 2) and did not increase following 3 years treatment. Periorbital tissue pigmentation has been reported to be reversible in some patients.~~

- Section 4.8

The following adverse reaction(s) should be added under the SOC Eye disorders with a frequency **very common**:

Prostaglandin analogue periorbitopathy

The following adverse reaction(s) should be removed:

~~Periorbital and lid changes including deepening of the eyelid sulcus~~

The following description should be added under a subheading 'Description of selected adverse events' below the adverse reactions table(s)

Description of selected adverse reactions

Prostaglandin analogue periorbitopathy (PAP)

Prostaglandin analogues including LUMIGAN can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with LUMIGAN, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.

Iris hyperpigmentation

Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish. Neither naevi nor freckles of the iris appear to be affected by the treatment. At 12 months, the incidence of iris hyperpigmentation with bimatoprost 0.1 mg/ml eye drops, solution was 0.5%. At 12 months, the incidence with bimatoprost 0.3 mg/ml eye drops, solution was 1.5% (see section 4.8 Table 2) and did not increase following 3 years treatment.

2.5 Usage

See page 2 of the report for usage information obtained from the Ministry of Health's pharmaceutical data web tool.

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Patchinsky et al, 2022 Dermatological adverse effects of anti-glaucoma eye drops: a review. [17]

The authors aimed to review the dermatological adverse effects secondary to the active agents in anti-glaucoma eye drops through a literature review. In January 2020, they queried PubMed. The initial search identified 1128 studies. After adding 38 linked studies, the authors analysed 123 studies. 46 cases of prostaglandin analogue periorbitopathy were identified with a mean time of onset of 31.2 months. Five patients recovered after eyedrop withdrawal and one improved.

One study studied PAP in 134 patients receiving latanoprost, bimatoprost or travoprost in only one eye for at least three months. They saw that PAP occurred more frequently in older patients (OR 3.0 [1.2–7.8]), in bimatoprost users (OR 4.0 [1.6–9.5]), and in travoprost users (OR 3.3 [1.1– 10.1]). Another study looked at DUES healing in 25 patients exposed to bimatoprost for at least 6 months. 15 patients (60%) developed DUES. 13 were switched to latanoprost and of them 11 (85%) improved or recovered after six months.

The table below shows the case reports and case series of local unusual cutaneous adverse events (AE) of anti-glaucoma eye drops.

Table 5 Case reports and case series of local unusual cutaneous AE of anti-glaucoma eye drops



3.1.2 Sano et al, 2022 Shortening of interpupillary distance after topical prostaglandin analog eye drop application in an ophthalmic surgeon: A case report [18]

This is a case report reporting on a case of interpupillary distance (IPD) shortening after prostaglandin analogue eye drop administration. The patient is a 36-year-old ophthalmic surgeon from Japan with open-angle glaucoma using eye drops bilaterally. The patient had been recording his IPD and it had been stable before the use of prostaglandin analogue drops. The patients IPD had shortened with latanoprost use and shortened further once switched to bimatoprost. The IPD partially recovered after several months following medicine discontinuation. This is shown in the figure below and consistent with previous studies.

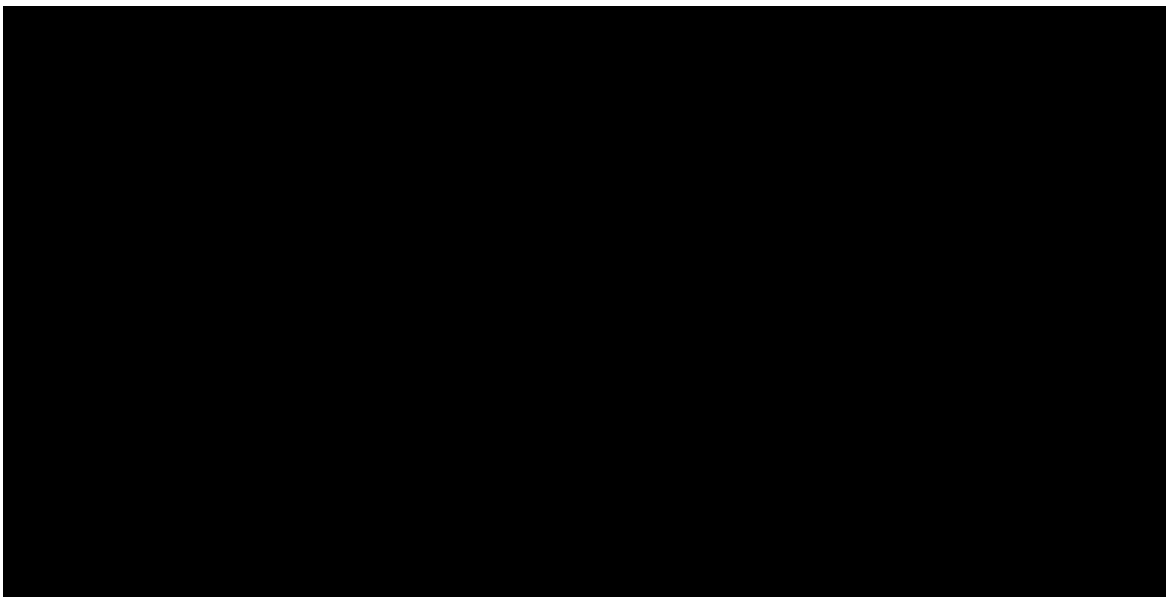


Figure 5 The line graph shows changes in interpupillary distance (IPD) over time with the topical use of prostaglandin analogues (PGAs). The solid line indicates IPD measured manually using a microscope in 0.5-mm units. The outlined white dot and dotted line indicate IPD measured using automatic refractometry. The bar above the graph indicates the PGA used and the duration of use; given below these are the other glaucoma drugs used. The IPD decreases to 62.5 mm. After switching to bimatoprost, the IPD decreased to 60 mm and then recovered upon switching back to latanoprost from bimatoprost.

This case notes that IPD shortening can occur due to PAP and it may be related to fat atrophy and the inhibition of adipogenesis. The authors note that the patients DUES was most obvious when his IPD was the shortest. This case reports notes that at least partial reversible changes in IPD occur with the use, switching and discontinuation of prostaglandin analogue eye drops.

3.1.3 Arranz-Marquez and Teus, 2020 Re: Kim et al.: Prostaglandin-associated periorbitopathy in children and young adults with glaucoma [21]

The authors consider the article by Kim et al offers an insight on the incidence and characteristics of these new kinds of periorbital side effects in both children and in young adults. Based on the results presented by Kim et

al, it seems that prostaglandin-associated periorbitopathy could be at least as common in younger patients as it is in adults. This is the opposite to what Arranz-Marquez and Teus found in their study which was that older patients seemed more prone to developing iris darkening than younger people (see section 3.1.21).

3.1.4 Kim et al, 2020 Prostaglandin-associated periorbitopathy in children and young adults with glaucoma [19]

This prospective cross-sectional cohort study evaluated relative palpebral and orbital changes after long-term unilateral exposure to prostaglandin analogues in patients with childhood glaucoma. The participants were 29 patients who had been treated unilaterally with prostaglandin analogues for at least 12 months.

Methods

Standard clinical photographs were taken at study enrolment which were then reviewed by experienced oculoplastic surgeons to determine which eye they believed to be treated unilaterally with a prostaglandin analogue. Each rater was also asked to determine whether other PAP symptoms were present.

Most of the patients were white (n=25, 86%), approximately half were male (n=15) and the median age at the time of the photographs was 14.7 years (IQR: 10.7 – 17.3 years).

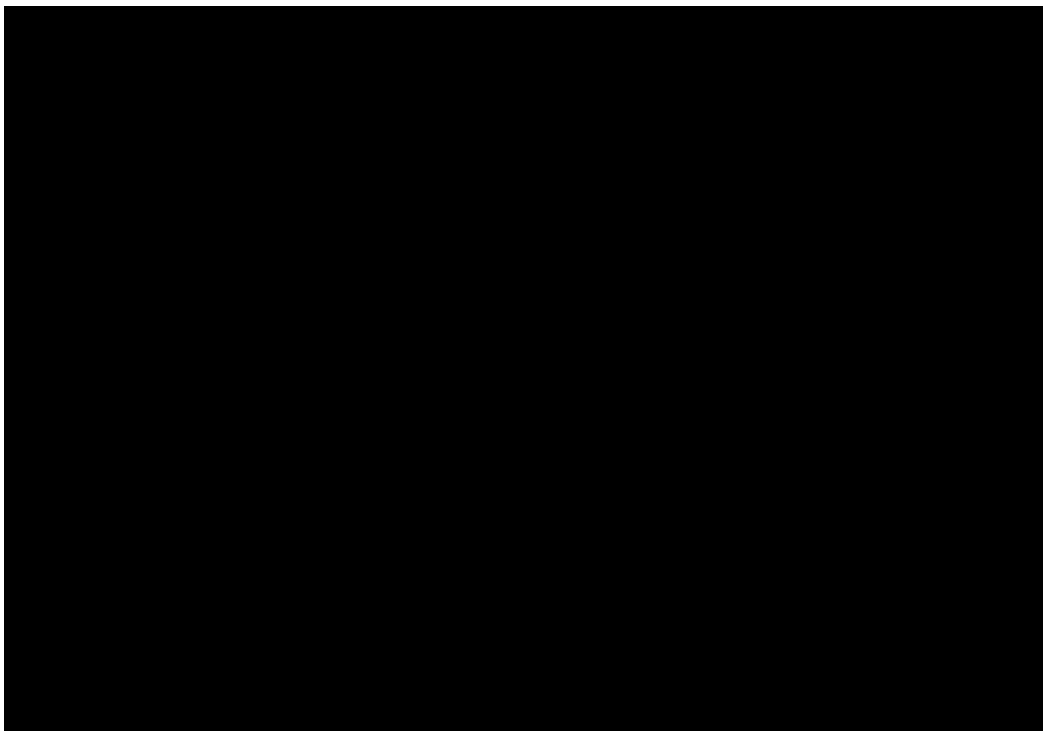
Results

Median unilateral PGA exposure time was 31.7 months (interquartile range: 18.8 - 44.3 months). The most commonly observed features of PAP were eyelash trichomegaly and hypertrichosis (n = 22, 76%), high upper eyelid crease (n = 20, 69%), upper eyelid ptosis (n = 14, 52%), and hollowing of the superior sulcus (n = 15, 52%).

Most of these changes were mild, but 20% to 30% of patients exhibited moderate eyelash and/or eyelid changes. One patient had severe PAP after long-term unilateral travoprost use. Group consensus with correctly selected laterality was achieved in all patients. The inter-rater reliability was excellent (k = 0.815, P < 0.001, 95% confidence interval [0.605, 1.000]).

The relative ocular, palpebral and orbital changes in children and young adults with glaucoma after long-term unilateral PGA exposure are listed in Table 6.

Table 6 Relative Ocular, Palpebral, and Orbital Changes in the Prostaglandin Analogue-Treated Eye of Children and Young Adults with Glaucoma After Long-Term Unilateral Prostaglandin Analogue Exposure (n = 29)



Deepening of the superior sulcus was observed in 52% of patients unilaterally treated with a prostaglandin analogue and fortunately these changes were typically mild. Most patients in this study were exposed to latanoprost only and therefore the proportion of patients with DUES could not be stratified by prostaglandin analogue type.

Conclusions

Other limitations of this study as mentioned by the authors were that it is a small cross-sectional cohort study and although most of the patients were white, the study included different ethnic groups with different periocular and other facial features. Not every patient had bilateral symmetric disease and could differ due to differences in glaucoma severity, degree of buphthalmos and or surgical history. Most patients were treated with latanoprost which has been associated with milder forms of PAP and which may explain the milder changes seen in children and young adults in this study. Lastly, the authors note that slight variations in the lighting conditions for the photographs may impact grading of PAP features.

The authors conclude that changes can occur in children and young adults treated with prostaglandin analogues. They note PAP has likely been under-reported as the changes are typically mild and often bilateral. Prostaglandin analogues are likely to continue to be used due to their tolerability and ability to achieve and maintain intraocular pressure control however patients and their families should be educated about the possible effects of prostaglandin analogues on periocular structures. The authors note a study by Kucukevcilioglu et al which reported more patients experienced DUES when being unilaterally treated with bimatoprost (80%) than travoprost (45%) or latanoprost (16%). Consistent with the findings in this study, Kucukevcilioglu et al also saw that milder changes of PAP were more frequently seen in patients treated with latanoprost (62%) than those treated with bimatoprost (7%) or travoprost (36%).

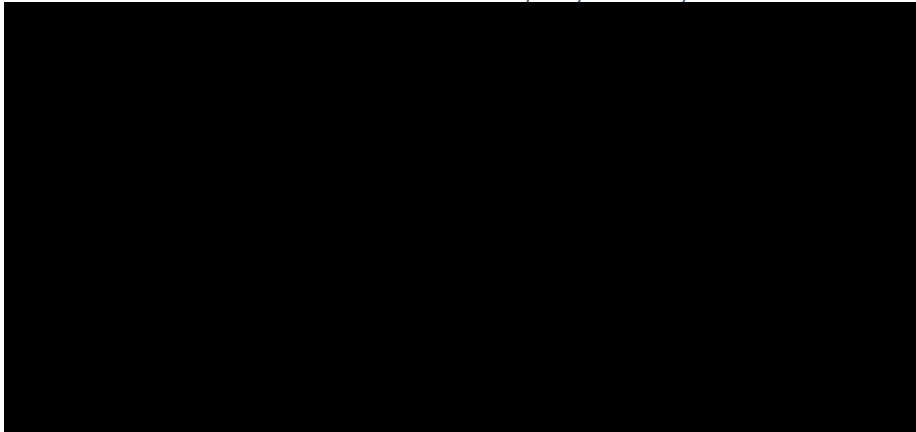
3.1.5 Sano et al, 2019 Shortening of Interpupillary Distance after instillation of Topical Prostaglandin Analog Eye Drops [22]

This retrospective comparative case series aimed to investigate changes in the interpupillary distance (IPD) after topical prostaglandin analogues in glaucoma patients as an objective indicator of PAP. 152 patients with glaucoma were enrolled. The patients had visual acuities exceeding 10/20 bilaterally and no intraocular

surgery during observation. IPDs were measured by automatic refractometry. The subjects were using bimatoprost, travoprost, latanoprost and tafluprost. 61 untreated patients were the controls.

The subjects in this study were 64 men and 8 women with an average age of 60.9 ± 10.6 years (range, 29-75 years). 14 subjects instilled bimatoprost, 25 travoprost, 55 latanoprost and 58 subjects instilled tafluprost bilaterally. This information can be seen in Table 7 below.

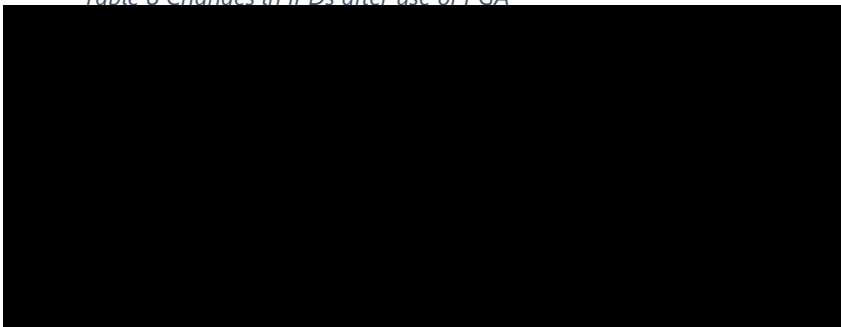
Table 7 General Characteristics and Number of Subjects Using Each PGA



The intraocular pressure and IPD were measured at each visit, before and after continual medicine administration (2-24 months).

The changes in IPDs after the use of prostaglandin analogues can be seen in the following table. Bimatoprost was associated with a significantly greater IPD change than the other prostaglandin analogues.

Table 8 Changes in IPDs after use of PGA



The study showed a significant decrease in the IPD after topical prostaglandin analogue instillation and could be used for objective monitoring of PAP in patients using prostaglandin analogues.

3.1.6 Di Staso et al, 2018 *In vivo* analysis of prostaglandin-induced ocular surface and periocular adnexa modifications in patients with glaucoma [16]

This review aimed to summarise the current knowledge about systemic side effects of prostaglandin analogues on periocular structures and ocular surface. PubMed was used to perform a comprehensive literature search. 70 articles were included in this review.

The authors discussed the results in groups of periocular changes. With relation to PAP, the first report of PAP in bimatoprost users was in 2004. In this report, PAP was described as 'deepening of the upper eyelid sulcus' (DUES). Subsequently, the presence of DUES was observed in travoprost, latanoprost and tafluprost users.

The incidence of DUES was found to be significantly higher in patients treated with bimatoprost (60%) compared to latanoprost (6%) and travoprost (53%). Bimatoprost-induced DUES was found to be at least partially reversible after drug interruption or change and symptoms reduced or disappeared in 85% of patients who switched from bimatoprost to latanoprost.

Di Staso et al note that, in addition to DUES, PAP also includes other clinical findings:

- Absence of dermatochalasis
- a deep crease and ptosis of the upper eyelid
- decreased prominence of the inferior orbital fat pads
- enophthalmos
- orbital fat atrophy
- flattening of the lower eyelid bags
- inferior scleral show
- tight orbits.

Travoprost use and older age were found to be risk factors for PAP. The authors also noted most of the mechanism of action evidence suggests PAP results from orbital fat atrophy, deriving from FP receptor stimulation-induced lipolysis and adipogenesis inhibition. Differences in the mechanism of action of bimatoprost, travoprost and latanoprost may also explain differences in the amount of orbital fat atrophy of prostaglandin analogue subtypes given that bimatoprost shows a higher incidence of PAP and has a dual mechanism of action as it stimulates both FP and prostamide FP receptors. Differences in pharmacokinetics and receptor affinity may also have a role to play in the differences seen between the prostaglandin analogue subtypes.

Comment:

The authors note that differences in the mechanism of action between bimatoprost and other prostaglandin analogues may be a reason for seeing a higher incidence of PAP with bimatoprost, however the incidence of DUES wasn't much greater with bimatoprost compared to travoprost.

3.1.17 Karli et al, 2018 Effect of prostaglandin analogs on matrix metalloproteinases and tissue inhibitor of metalloproteinases in eyelid muscle specimens [23]

The purpose of this study was to characterise the effect of prostaglandin analogues on tissue specific expression of matrix metalloproteinases (MMP) and tissue inhibitor of metalloproteinases (TIMP) in levator aponeurosis resections (elevation of the eyelid) and conjunctiva-Muller muscle resections (a posterior eyelid ptosis repair technique).

MMPs have been shown to influence normal adipogenesis in animal models and prostaglandin analogues may contribute to PAP through alterations of MMP/TIMP dynamics and subsequent extracellular matrix (ECM) turnover. MMPs and TIMPs remodel the ECM by modifying the structure and activity of substrates that are key players in maintaining ocular and periorbital physiology. A dysregulation in the ECM has been thought to influence PAP-associated characteristics.

Immunohistochemistry was used to analyse specimens from levator aponeurosis resections and conjunctiva-Muller muscle resections of prostaglandin analogue users and non-users for tissue specific expression of MMPs and TIMP-2. Patients undergoing ptosis repair were selected based on inclusion and exclusion criteria.

Overall differences in tissue specific expression of MMPs and TIMP could only be made on eight samples that had complete muscle, collagen and adipose measurements. Given the small sample size, there was no statistically significant difference in MMP/TIMP expression with prostaglandin analogue exposure when either tissue samples were considered separately, although a different expression distribution was seen.

The article concluded that prostaglandin analogue exposure may affect MMP and TIMP expression in a tissue specific manner. Decreased expression of certain MMPs in collagen correlates to increased clinical measures of PAP. Further studies with larger samples are needed to ascertain if the changes associated with PAP are due to MMP/TIMP changes or to structural changes. The authors also noted that immunohistochemistry may not be sensitive to detecting subtle differences in enzymatic levels.

3.1.8 Patradul et al, 2017 Factors related to prostaglandin-associated periorbitopathy in glaucoma patients [13]

This cross-sectional study aimed to determine factors related to PAP and its prevalence in glaucoma or ocular hypertension (OHT) patients using prostaglandin analogues.

134 eligible subjects from the general ophthalmology and glaucoma outpatient clinic of the Department of Ophthalmology, King Chulalong-korn Memorial Hospital in Thailand were enrolled in the study. Patients were those diagnosed with glaucoma or OHT who had been using prostaglandin analogues with or without timolol to lower intraocular pressure for at least three months and aged 18 years or older. A digital camera was used to take photographs of the patients' eyes. This study looked at multiple clinical characteristics of PAP, not only DUES as in some other studies. The characteristics were:


- DUES
- absence of dermatochalasis
- a deep crease in the upper eyelid
- ptosis of the upper eyelid (defined as position of the upper eyelid more than 2 mm inferior to the upper limbus)
- decreased prominence of the inferior orbital fat pads
- inferior scleral show
- enophthalmos
- orbital fat atrophy.

Patients were diagnosed with PAP if they had DUES (major clinical appearance) with at least three of the additional clinical appearances.

Two specialists independently evaluated the photos.

A total of 134 subjects were enrolled, with 59 men and 75 women. Mean age was 66.0 ± 11.4 years (range, 35 to 91 years), with 36 patients (26.9%) younger than age 60 and 98 patients (73.1%) older than 60. Demographic characteristics can be seen in the table below.

Table 9 Demographic data



The prevalence of PAP in this study was 44.8% (95% CI, 36.3–53.3%). In univariate analysis, PAP was more common in bimatoprost and travoprost compared with latanoprost. In multivariate analysis, the factors significantly associated with PAP were bimatoprost (OR, 4.0; CI, 1.6–9.5) and travoprost (OR, 3.3; CI, 1.1–10.1) when compared with latanoprost (the first PGA), age greater than 60 years (OR, 3.0; CI, 1.2–7.8), and timolol (OR, 2.9; CI, 1.3–6.8).

Intra-observer reliability for PAP diagnosis was good between the two glaucoma specialists ($\kappa = 0.82$).

The associations with each factor can be seen in the table below.

This study showed that timolol may precipitate periorbital change when used in addition to prostaglandin analogues however the authors noted that the mechanisms involved in timolol precipitating PAP are not clearly understood and further studies are needed. The authors noted that in patients receiving bilateral prostaglandin analogues, PAP may be more difficult to detect however pre-treatment evaluation and observation of periorbital change is needed. Patients should also be informed about this side effect at the start of treatment.

Limitations of the study include the design being cross-sectional which meant the authors could not observe patients from the beginning of prostaglandin analogue use and the incidence of PAP could not be evaluated. The photographs also limit the ability to detect certain characteristics such as DUES and enophthalmos and lastly PAP was diagnosed by clinical appearance which is subjective and depends on the evaluators experience.

3.1.9 Abalo-Lojo and Gonzalez, 2016 Editorial: Prostaglandin associated periorbitopathy [24]

The authors note prostaglandin analogues are first choice medicines for glaucoma with reversible and irreversible side effects. The authors state the following are reversible side effects:

- conjunctival hyperaemia
- increased periocular skin pigmentation
- changes in eyelids (increased length, thickness, pigmentation and number of eyelashes).

Irreversible side effects are noted as increased iris pigmentation.

In 2004, cases of deepening of the superior palpebral furrow were seen in three patients being treated with bimatoprost. Subsequently, other prostaglandins were also related to deepened upper palpebral furrow.

The authors state that it has recently been demonstrated that prostaglandin analogues inhibit adipogenesis by stimulating the FP receptor of the F_{2α} prostaglandin (see Figure 4).

As many others have noted, PAP is used to describe a number of orbital tissue changes that can arise with the topical use of prostaglandin analogues.

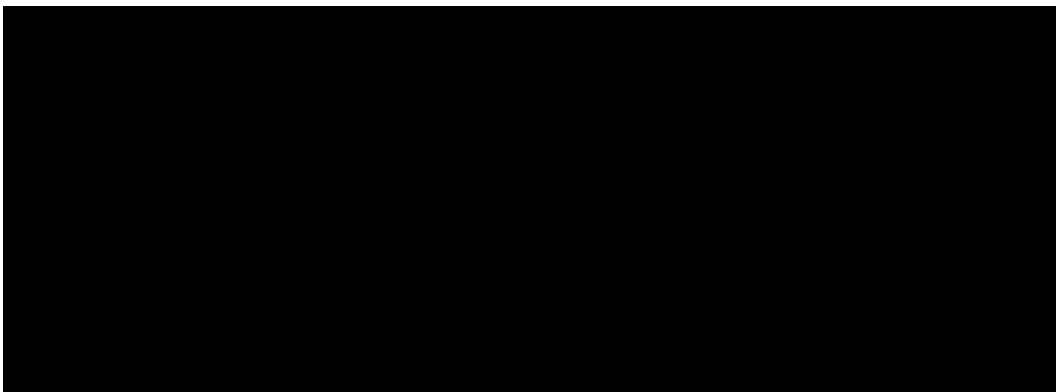
3.1.10 Nakakura et al, 2015 Prostaglandin-associated periorbitopathy in latanoprost users [25]

This study investigated the incidence of PAP in subjects with glaucoma treated with latanoprost ophthalmic solution.

Between January and June 2014, glaucoma patients who had been treated with latanoprost for more than one year at a hospital in Japan were recruited. One eye and the forehead in 22 subjects were included in this cross-sectional retrospective study. All patients had used latanoprost for more than 1 year (range, 12 to 45 months; mean, 26.0 months) and were prostaglandin F_{2α} analogue treatment-naïve at the beginning of latanoprost therapy. Digital photographs of the subjects' eye and forehead were taken before latanoprost therapy and at the last examination to evaluate the side effects of treatment. Four signs of PAP and three supplemental side effects around the eyelids were judged to be negative or positive by three independent observers. If the observers unanimously rated a sign as positive, the result was defined as positive.

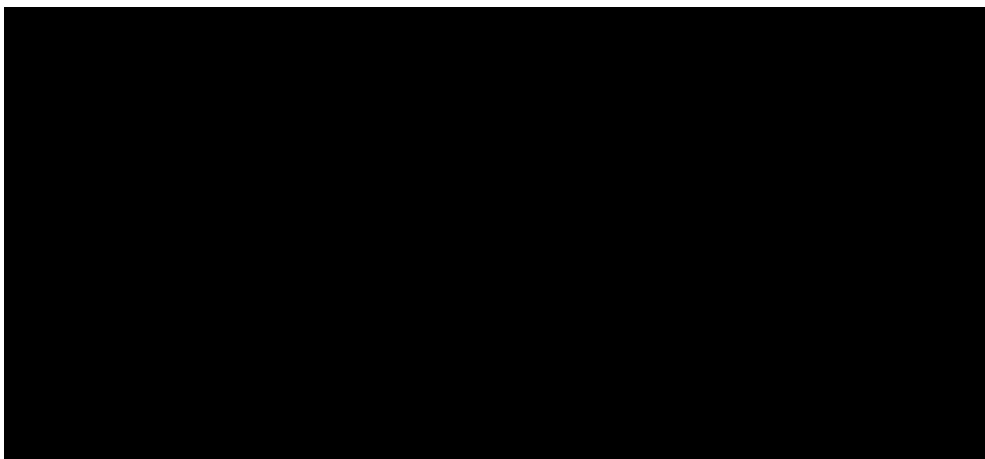
Patient characteristics can be seen in the table below.

Table 11 Patient demographics



The table below shows the interobserver agreement for the seven signs. DUES exhibited the best agreement (κ coefficient = 0.618), whereas eyelash growth demonstrated the worst agreement (κ coefficient = -0.048).

Table 12 Interobserver agreement for the seven signs

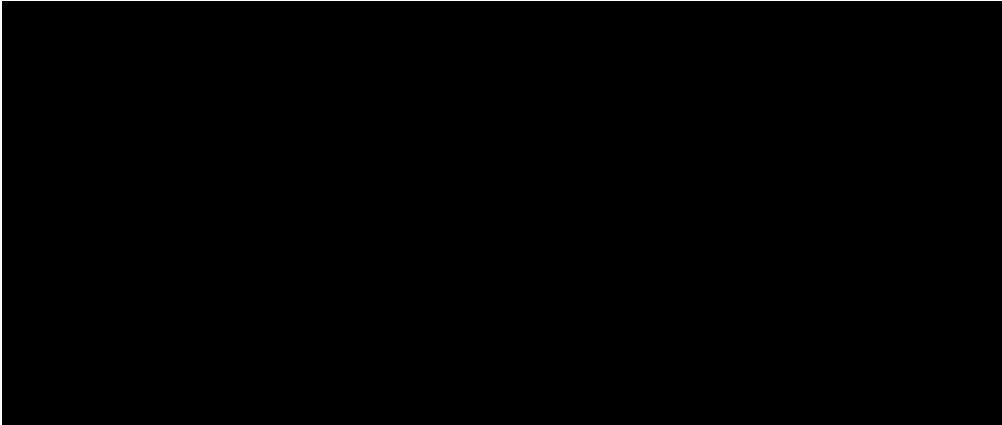


Twelve subjects (54.5%) had no apparent signs. Three subjects were judged to have DUES (13.6%), and two subjects each were judged to have flattening of the lower eyelid bags and eyelid pigmentation (9.0%). The other signs were judged as positive in only one subject each, respectively (4.5%). A univariate logistic

regression analysis showed no significant associations between any of the signs and age, sex, or the duration of therapy.

The incidence of PAP signs and supplemental side effects can be seen in the table below.

Table 13 Incidence of PAP signs and supplemental side effects



Limitations of this study include variations in the colour of photographs which might have affected the judgement of the observers and the strict definition of a positive judgement which resulted in a low incidence of side effects.

Latanoprost induced DUES, upper eyelid ptosis, flattening of the lower eyelid bags, inferior scleral show, and supplemental side effects around the eyelids have been reported; however, the rates of such occurrence might be relatively low.

3.1.11 Rabinowitz et al, 2015 Unilateral prostaglandin-associated periorbitopathy: A syndrome involving upper eyelid retraction distinguishable from the aging sunken eyelid [4]

This prospective cohort study aimed to study the effects of prostaglandin analogue drops on the eyelids and adnexa (the tissues surrounding the eyeball) in unilaterally treated subjects with the intention of qualifying, quantifying, and categorizing the characteristics of PAP.

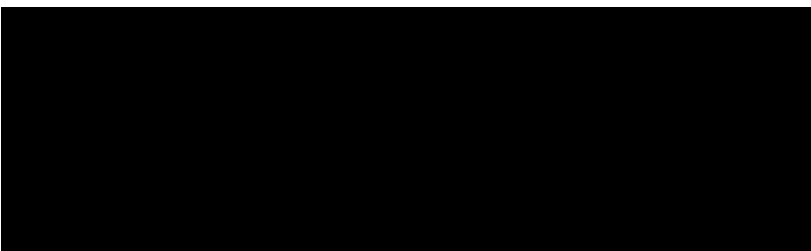
Patients treated in the Wills Eye Hospital Glaucoma Department with prostaglandin analogue drops in only one eye, for ocular hypertension and/or glaucoma, for at least one year were offered enrolment. The authors developed a novel PAP grading system by stratifying treated eyelids and adnexa into 3 categories:

- grade I involves relative fat atrophy without superior sulcus deformity (SSD)
- grade II includes fat atrophy with a grade II SSD
- grade III is positive for both relative fat atrophy and severe, or grade III, SSD.

All patients had photographs taken which were analysed by three researchers and grades given to each eye. Participants were also given a short questionnaire where they could comment on whether they had experienced any side effects or were unhappy with the appearance of their eyelids.

33 patients were enrolled in this study with an equal number of patients on latanoprost, travoprost and bimatoprost. The patient demographics can be seen in the table below.

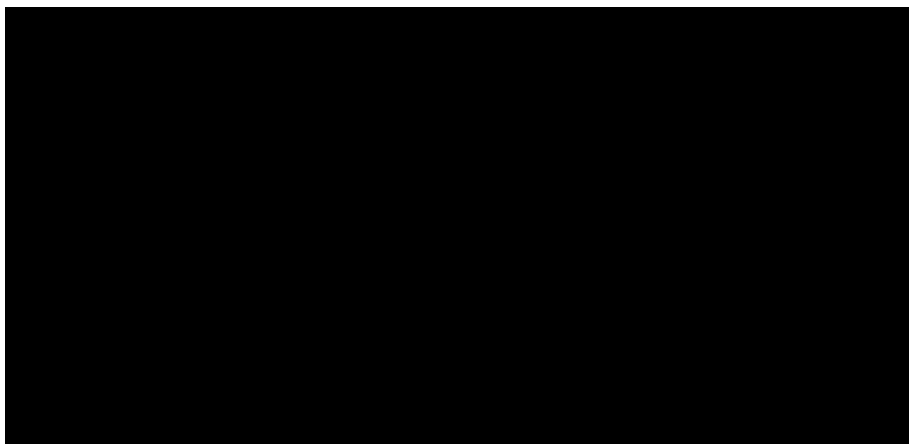
Table 14 Patient demographics



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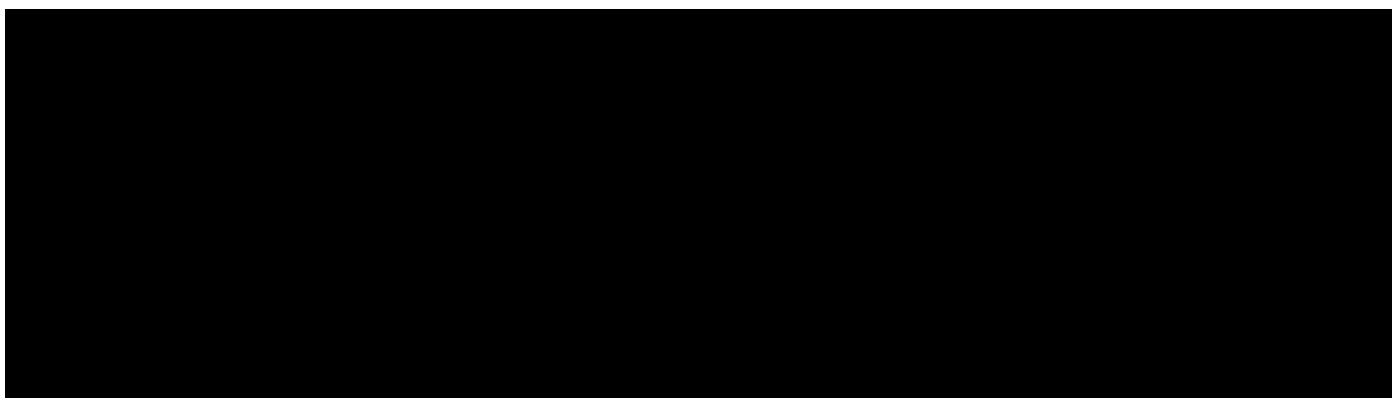
Nine of 33 (27%) patients noticed a change in the appearance of their treated eyelid and adnexa, and five of 33 (15%) patients were unhappy with the appearance of their treated side. Treated eyes had statistically significantly more lagophthalmos (incomplete or defective closure of eye lids) (0.62 mm, $p < 0.001$), SSD/PAP grade (0.72, $p < 0.001$), upper eyelid retraction (0.89 mm, $p=0.02$) and eyelid redness (1.08, $p < 0.001$) compared with untreated eyes. A comparison of measurements between treated and untreated eyelids can be seen in the table below.

Table 15 Comparison of measurements between treated and untreated eyelids



Lagophthalmos (inability to close eyelids completely) and redness were significantly increased in patients on bimatoprost when compared with latanoprost and travoprost. Bimatoprost and travoprost patients averaged worse SSD and PAP grade than latanoprost patients. Although not statistically significant for all three prostaglandin analogue drops, the mean vertical palpebral fissure length, amount of enophthalmos and degree of upper eyelid retraction were noticeably greatest in bimatoprost-treated eyes. See table below for the difference between treated and untreated eyes for the different eye drops.

Table 16 Results by drop, difference between treated and untreated eyelids



This study showed upper eyelid retraction (not ptosis) to be a significant feature of PAP which is in contrast to most other studies. This study was limited by the relatively small sample size.

As with other authors, these authors note that awareness of PAP is essential as eyes may be affected even in the absence of patient recognition.

3.1.12 Kucukevcilioglu et al, 2014 Prostaglandin-associated periorbitopathy in patients using bimatoprost, latanoprost and travoprost [26]

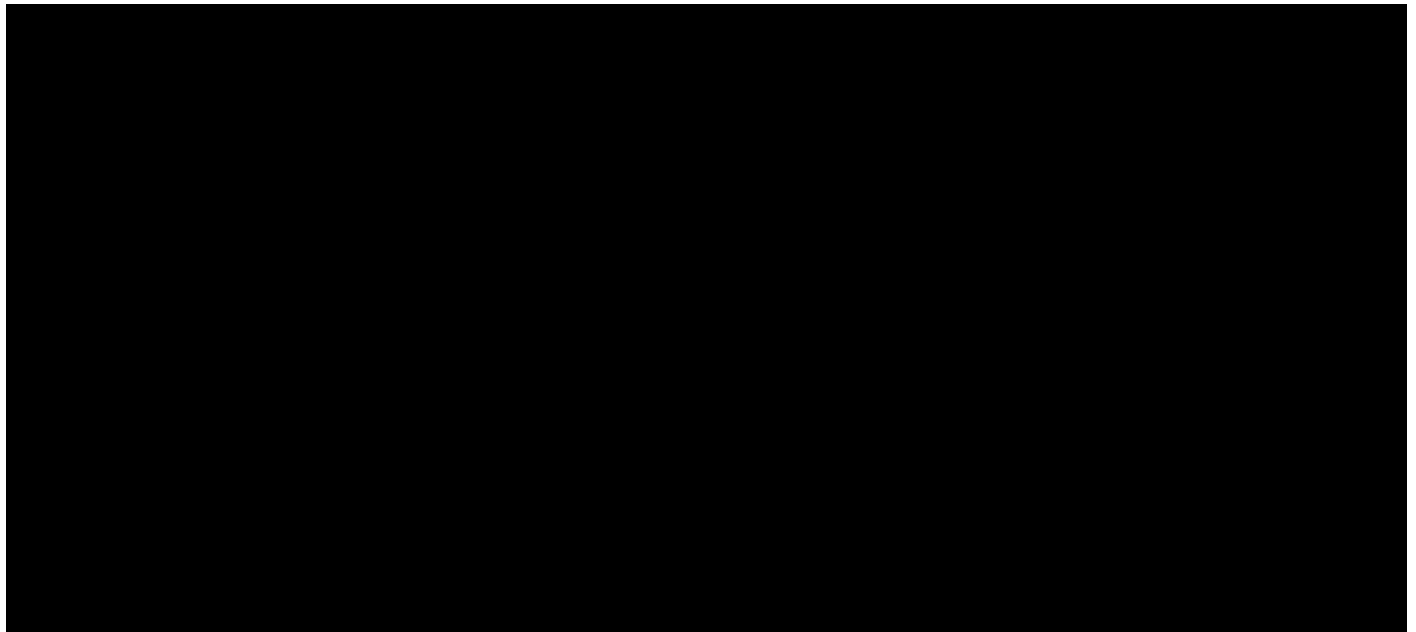
The aim of this retrospective observational case series was to investigate the frequency of PAP among bimatoprost, latanoprost and travoprost users. There were 105 participants who were using one of the medicines in one eye for more than one month. The other eye was used as a control. A careful history and physical examination were performed to exclude conditions that may have contributed to periocular findings. None of the patients had used the other prostaglandin analogues in the one year prior to the assessment. The

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patients had routine visits are were blinding evaluated for the presence of PAP findings which were upper lid ptosis, deepening of the upper eyelid sulcus, dermatochalasis involution, loss of the periorbital fat pad and enophthalmos. An agreement between two out of the three ophthalmologists was required for a decision on each PAP finding.

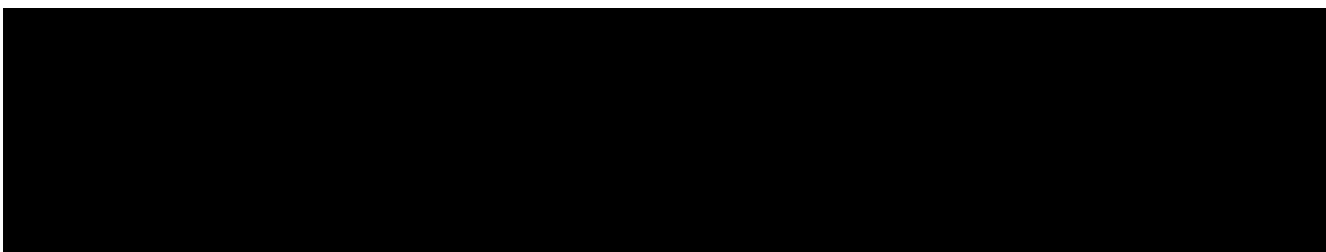
Out of the 105 patients, 15 were in the bimatoprost group, 70 patients were in the latanoprost group and 20 patients in the travoprost group. Patient characteristics can be seen in the table below. There was a significant difference with respect to drug co-use ($P < 0.01$), which was least frequent among Travatan users. There were no significant differences among the groups with respect to age, gender, laterality, glaucoma type and duration of drug use ($P > 0.05$). The duration of use varied widely.

Table 17 Baseline patient characteristics




57 of the 105 patients (54.2%) had at least one of the PAP findings. The differences in the frequency of PAP findings between groups were statistically significant. The frequencies were 93.3% (14 patients) in the bimatoprost group, 70% (14 patients) in the travoprost group and 41.4% (29 patients) in the latanoprost group ($P < 0.01$). The most frequent of all PAP findings was the loss of the periorbital fat pad, followed by dermatochalasis involution, deepening of the upper lid sulcus, enophthalmos and upper lid ptosis in a decreasing order. The differences in the frequencies of these PAP findings between groups were statistically significant. They were most frequent in the bimatoprost group and least frequent in the latanoprost group ($P < 0.05$). The table below shows the percentage of PAP between the study groups.

Table 18 Comparison of percentage of PAP and PAP findings in study drug groups



The distribution of PAP patients according to severity can be seen in the figure below.



The authors mention different proposed mechanisms of PAP and state that the exact mechanism has not been established. First it was believed that DUES was a result of either fibrosis or atrophy of Mullers muscle induced by prostaglandins. Then it was postulated that atrophy of the preaponeurotic and deep orbital fat pads is the causative mechanism for all the observed side effects except upper lid ptosis. Another possible mechanism relates to prostaglandins and prostamides inducing the activation of matrix metalloproteinases which ease the outflow of aqueous humour resulting in fewer collagen fibres and the degeneration of fat in the levator complex. However, as ptosis was still noted after the resolution of sunken eye appearance, they suggested prostaglandin-induced lipolysis as a possible mechanism. Another study reported pathological findings suggestive of fat atrophy which was not significantly different in the latanoprost group compared to travoprost and bimatoprost groups.

In conclusion, in a Caucasian population, this study suggests that PAP is as frequent as other local side-effects among prostaglandin users and seems to be more severe in bimatoprost users. The loss of the periorbital fat pad is the first sign to occur during the evolution of PAP, especially in older patients.

3.1.13 Maruyama et al, 2014 Incidence of deepening of the upper eyelid sulcus after topical use of travoprost ophthalmic solution in Japanese [27]

The purpose of this prospective study was to investigate the deepening of the upper eyelid sulcus (DUES) with topical use of travoprost in Japanese glaucoma patients.

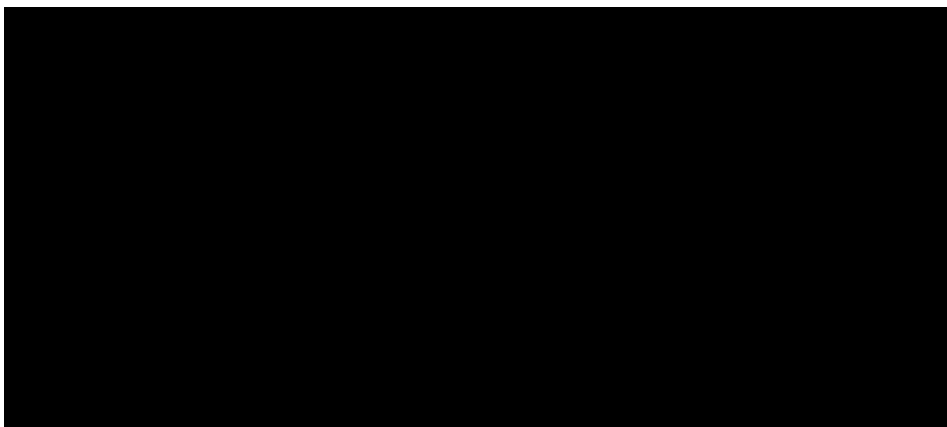
32 patients who had been treated topically with travoprost unilaterally for six months at baseline and started treated in both eyes were included in the study.

Patients had visits at two, four and six months. At each visit photographs of both eyes and forehead were displayed randomly. The presence of DUES was diagnosed when three examiners unanimously rated the case as positive. Patients were also asked at each visit if they noticed any symptoms of DUES subjectively.

All 32 patients completed six months of evaluation and no patient discontinued travoprost before the six months because of subjective DUES symptoms or other complications. The mean age of the patients was 51.6 ± 14.2 years and the age ranged from 26 to 86 years.

DUES was detected objectively in 34% (11/32), 53% (17/32), and 53% (17/32) of the patients after 2, 4 and 6 months, respectively, of treatment. There was no new onset of DUES after 4 months. The incidence was significantly higher in older patients ($P < 0.05$) but not related to sex, refraction, pre-treatment and post-treatment intraocular pressure and intraocular pressure reduction (see table below). 41% (7/17) of patients with objectively diagnosed DUES noticed the presence of DUES by themselves.

Table 19 Comparison of factors affecting the incidence of DUES



The authors concluded DUES is a common side effect of topical travoprost treatment in Japanese glaucoma patients.

3.1.14 Sakata et al, 2014 Incidence of deepening of the upper eyelid sulcus in prostaglandin-associated periorbitopathy with a latanoprost ophthalmic solution [28]

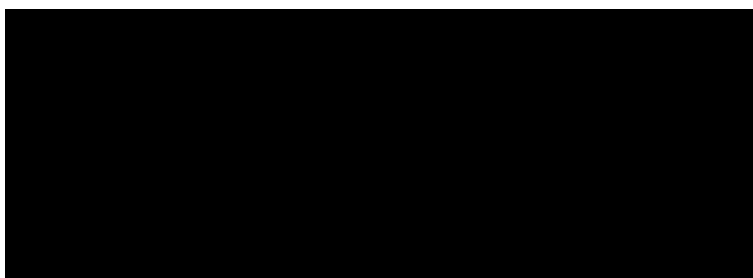
This open-label prospective study investigated the incidence of DUES in Japanese open-angle glaucoma patients initially treated with latanoprost ophthalmic solution.

Facial photographs were taken and subjective reports of the recognition of DUES were obtained at the beginning of treatment and at 2, 4 and 6 months after. Three blinded investigators objectively evaluated the photographs. When the three observers agreed on the deepening of the palpebral in the same photograph, the patient was judged as DUES positive.

52 newly diagnosed open-angle glaucoma Japanese patients were evaluated (52 eyes). There were 28 males and 24 females. The objective rate of DUES was 1/52 (2%; 95% CI 0.05 to 10.7%) at 2 months, 2/52 (4%; 95% CI 0.5 to 13.9%) at 4 months, and 3/52 (6%; 95% CI 1.2 to 16.9%) at 6 months. During this period, no patient self-reported an occurrence of DUES. Latanoprost was also found to be successful at reducing intraocular pressure.

Because only slight changes in DUES were seen in only three patients in this study the degree of DUES seems to be mild in this short-term study. The authors also compared other studies done in Japanese glaucoma patients with other prostaglandin analogues (see table below).

Table 20 Summary of the objectively evaluated rate of deepening of the upper eyelid sulcus treated with four prostaglandin analogues by prospective studies in Japanese glaucoma patients



The frequency of DUES was always higher in bimatoprost and travoprost treatment compared with latanoprost and this may explain the recovery seen in some studies when patients switched from bimatoprost to latanoprost (see section 3.1.15). This study also confirms that latanoprost has a good intraocular pressure lowering effect. However, there are also limitations including the small sample size and the short follow-up period. As with other studies, assessment of DUES is subjective.

3.1.15 Taketani et al, 2014 Activation of the Prostanoid FP Receptor Inhibits Adipogenesis Leading to Deepening of the Upper Eyelid Sulcus in Prostaglandin-Associated periorbitopathy [29]

This study aimed to analyse the effects of all commercially available PGs on adipogenesis in vitro so as to clarify the mechanism of deepening of the upper eyelid sulcus (DUES). Primary cultured adipocytes from FP receptor knockout mice were used to investigate the role of FP receptors in adipogenesis.

3T3-L1 cells were used which is a universally used cell line for lipid studies. 3T3-L1 preadipocytes were treated to promote differentiation into mature adipocytes. 1 to 1000 nM latanoprost acid (LAT-A), travoprost acid (TRA-A), tafluprost acid (TAF-A), bimatoprost (BIM), bimatoprost acid (BIM-A), unoprostone (UNO), or prostaglandin F2a (PGF2a) was applied to cells during the early and late stages of differentiation (days 0, 2 and 7). Oil red O staining was used to detect intracellular lipids on day 10. Stained areas measured on a photograph were compared with those in control cultures. All experiments were performed in a masked manner. Similar experiments were then performed using primary cultured mouse adipocytes from FP receptor knockout and wild-type mice.

When prostaglandin analogues were added on day 0 or 2, LAT-A, TAF-A, BIM-A, and PGF2a significantly inhibited adipogenesis ($P < 0.01$ on day 0, $P < 0.05$ on day 2) at concentrations of 10 nM and 100 nM, and TRA-A inhibited adipogenesis only at 100 nM. Bimatoprost and UNO did not affect adipogenesis at any concentration. When PGs were added on day 7, 100 nM LAT-A, BIMA, or PGF2a significantly suppressed adipogenesis ($P < 0.05$). In mouse primary adipocyte cultures, LAT-A, TAF-A, BIM-A, TRA-A, and PGF2a significantly suppressed adipogenesis in wild-type adipocytes ($P < 0.05$), but adipogenesis was not suppressed by any of the PG compounds in FP knockout mouse adipocytes.

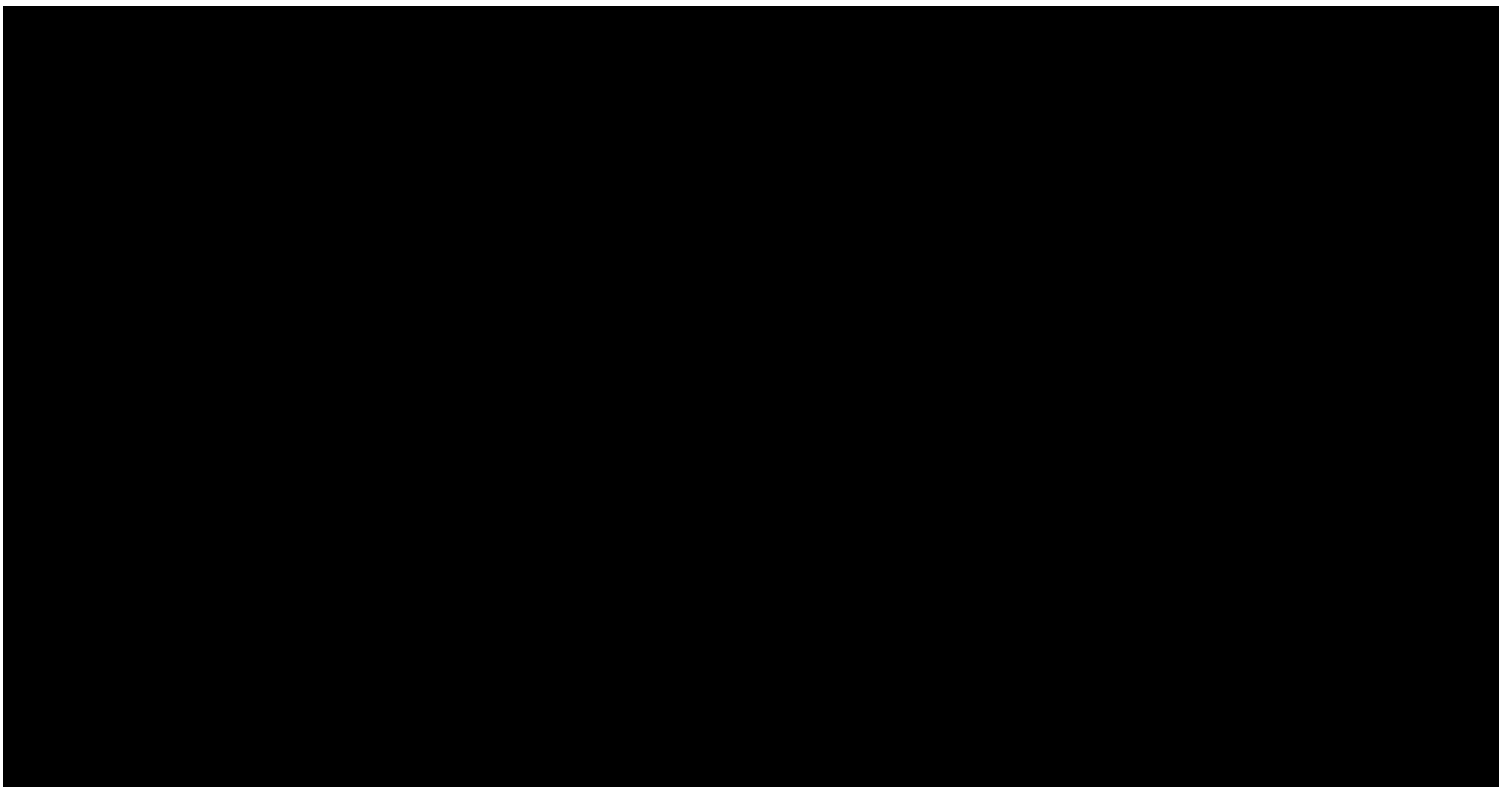


Figure 7 Dose-dependent effects of PGs on adipogenesis in primary cultured mouse adipocytes. Latanoprost acid, TAF-A, TRA-A, BIM-A, and PGF2a suppressed adipogenesis in a dose-dependent manner ($P < 0.05$ or 0.01), but BIM and UNO did not affect adipogenesis at all even at high concentrations (100 nM and 1000 nM). Travoprost acid affected adipogenesis only at 100 nM ($P < 0.05$). Latanoprost acid suppressed adipogenesis at 10 and 100 nM concentrations, but not at 1 nM ($P < 0.05$).

The authors discuss that this clinical and animal data suggest that the incidence of DUES may be influenced by differences in prostanoid and prostamide agonists or by the pharmacological affinity of these drugs for FP receptors.

The authors concluded that prostaglandin analogues have the potential to inhibit adipogenesis through FP receptor stimulation. Although these findings should be further analysed in model systems more closely related to orbital fat, PG analogues may directly lead to reduced orbital fat by inhibiting adipogenesis.

3.1.16 Inoue et al, 2013 Deepening of the upper eyelid sulcus caused by 5 types of prostaglandin analogues [30]

The aim of this study was to retrospectively examine the frequency of upper eyelid sulcus deepening caused by different types of prostaglandin eye drops in Japanese patients. The five types of prostaglandin eye drops used in Japan are latanoprost, travoprost, tafluprost, bimatoprost and isopropyl unoprostone.

250 patients (250 eyes, 105 men, 145 women) diagnosed with primary open-angle glaucoma or ocular hypertension and five healthy patients as controls were included in the study. The patient age ranged from 28 to 86 years (mean age 60.4 ± 11.6 y). The eye drops were administered in only one eye, the treated eye was not selected randomly as the study was retrospective and all subjects were treated with one of the five eye drops for greater than three months. None of the patients had used other prostaglandin analogues in the six months before the assessment. A single-lens reflex camera was used to photograph the open eyelids.

The mean patient ages were:

- Latanoprost - 62.1 ± 12.3 years (range, 32 to 86 y)
- Travoprost - 59.0 ± 11.7 years (range, 35 to 80 y)
- Tafluprost - 59.8 ± 11.0 years (range, 34 to 80 y)
- Bimatoprost - 58.8 ± 11.3 years (range, 28 to 83 y)
- Unoprostone - 62.4 ± 11.6 years (range, 35 to 83 y)

No significant differences were found among the groups ($P=0.3487$).

The number of people in each group were:

- Latanoprost – men 23, women 27
- Travoprost – men 20, women 30
- Tafluprost – men 26, women 24
- Bimatoprost – men 19, women 31
- Unoprostone – men 17, women 33

No significant differences were found among the groups ($P=0.3920$).

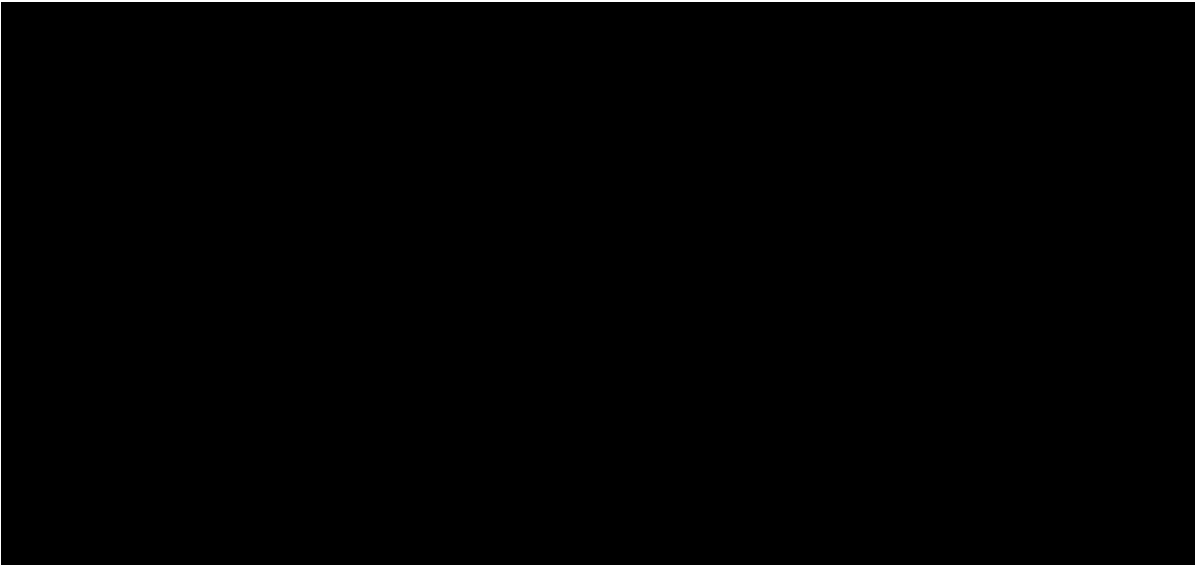
The mean administration period for the latanoprost group was significantly longer than that for the other groups, and that for the unoprostone group was significantly longer than that for the travoprost, tafluprost, and bimatoprost groups ($P<0.0001$).

Three ophthalmologists independently judged the appearance of the deepened upper eyelid sulcus in the photographs of the 250 patients and 5 controls by comparing the right and left eyes. Patients were also asked to complete a subjective self-reported symptom questionnaire.

Deepening of the upper eyelid sulcus objectively appeared in (see figure below):

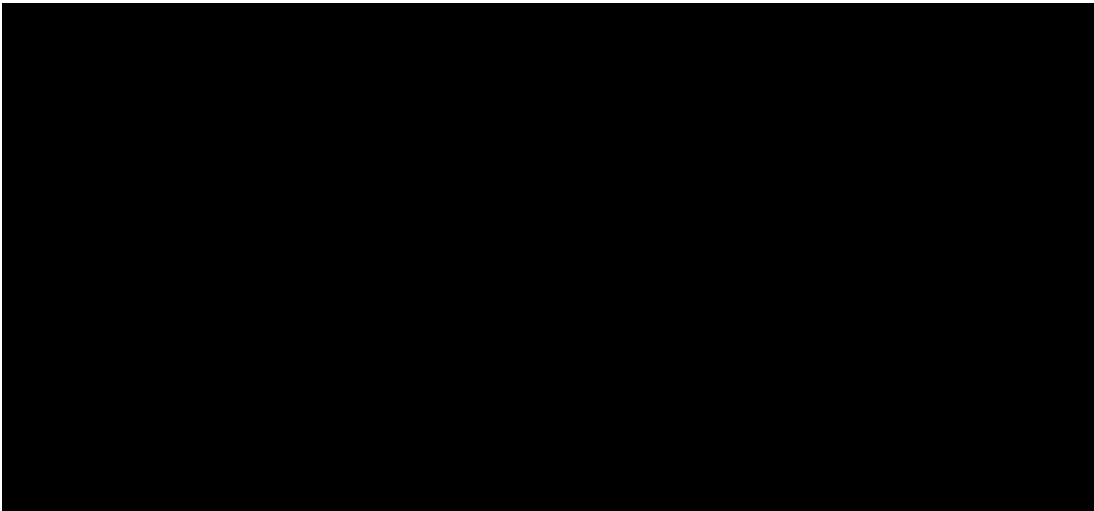
- 12 cases (24.0%) in the latanoprost group
- 25 cases (50.0%) in the travoprost group
- 9 cases (18.0%) in the tafluprost group
- 30 cases (60.0%) in the bimatoprost group
- 4 cases (8.0%) in the unoprostone group.

The deepening appeared more frequently in the travoprost and the bimatoprost groups ($P<0.0001$, χ^2 test) (see figure below).



*Figure 8 Objective evaluation of the deepening of the upper eyelid sulcus. The frequency of deepening in eyes in the bimatoprost group was significantly higher than that in the latanoprost, the tafluprost and the unoprostone groups (** $P < 0.0001$).*

In the self-reported questionnaire, the number of patients who reported deepening in the bimatoprost group was significantly higher than that in the latanoprost, tafluprost and unoprostone groups ($P = 0.0002$, χ^2 test) (see figure below).



*Figure 9 Subjective evaluation of the deepening of the upper eyelid sulcus. The eyes in the travoprost and the bimatoprost groups exhibited significantly more frequent deepening than those in the latanoprost, the tafluprost and the unoprostone groups (** $P < 0.001$).*

The authors noted that a major limitation in the present study is that if laterality in the original upper eyelid sulcus existed before eye drop administration, then the judgment of the deepening may be inaccurate. By previous studies comparing the appearance of the upper eyelid sulcus before and after administration, more accurate judgments can be made. This study investigated the difference between left and right eye sockets but did not evaluate the extent of deepening of the upper eyelid sulcus. In addition, administration periods for the different eyedrops varied, they were not standardised. The authors noted that patients who receive eyedrops for a long time may exhibit a stable condition and not notice the adverse effects.

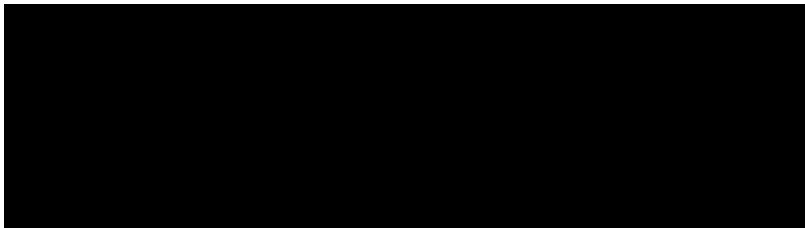
The authors concluded that upper eyelid deepening frequently occurred with bimatoprost use and this effect should be made clear before starting bimatoprost treatment.

3.1.17 Sakata et al, 2013 Recovery from deepening of the upper eyelid sulcus after switching from bimatoprost to latanoprost [31]

This prospective, observer-masked, open-label study investigated recovery from bimatoprost-induced DUES after switching to latanoprost treatment.

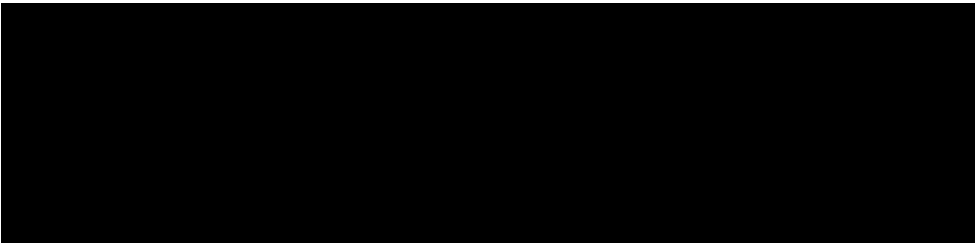
25 open angle glaucoma Japanese patients who had been treated with latanoprost in both eyes once daily for longer than 12 months were enrolled in the study. These patients also required further intraocular pressure reduction and latanoprost was switched to bimatoprost. Within six months, 15 of the 25 patients had developed objective DUES. Of these 15 patients, 13 agreed to revert back to latanoprost and had examinations including photographs taken at time points following the switch. DUES was seen to improve in 11 of the 13 patients (Table 21).

Table 21 The course of changes in objective DUES measurements after the switch back to latanoprost



When treatment was switched back to latanoprost, eight of the 13 patients were subjectively aware of their DUES. During latanoprost treatment, five out of eight patients (63%) reported improvement in DUES after 2 and 4 months and 6 (75%) reported improvement after 6 months (Table 22).

Table 22 The course of changes in subjectively reported DUES after the switch back to latanoprost



The authors reported on some limitations of the study including case selection bias. All patients were on latanoprost treatment for 12 months before starting bimatoprost and this previous treatment could have affected the development of DUES even though it may have gone unnoticed. The small sample size and lack of a control group made it difficult to determine factors affecting the reduction in DUES. The fact that only DUES was evaluated and the short duration of bimatoprost use are additional limitations. Possibly the reduction in DUES may not be seen in patients taking bimatoprost for a longer time. However, the authors conclude that bimatoprost-induced DUES may be reversible.

3.1.18 Shah et al, 2013 A cross-sectional Sectional Survey of the Association between Bilateral Topical Prostaglandin Analogue Use and Ocular Adnexal features [32]

This prospective cross-sectional study aimed to confirm whether PAP is clearly associated with prostaglandin analogue application among bilateral users (50 years and over). The subjects were 157 current, 15 past and 171 never users of prostaglandin analogues. A validated grading scheme was applied by masked observers and confirmed by clinical examination. Photos were assessed for upper lid dermatochalasis and lower lid steatoblepharon. Another masked clinical examiner also assessed upper lid ptosis, levator muscle function and inferior scleral show. Characteristics of the study participants can be seen in the table below.

Table 23 Characteristics of study participants

Multivariable analyses were performed to assess whether PAP was independently associated with prostaglandin analogue use or whether it was the result of confounding features (e.g. age, ethnicity, BMI or other glaucoma medications). Multivariable analyses indicated there was a 230-fold increased risk of incremental involution of dermatochalasis (odds ratio (OR) = 2.30; 95% confidence interval (CI) 1.43–3.69; $p = 5.44E-04$) and a 249-fold increased risk of incremental loss of lower lid steatoblepharon (herniation of the orbital fat in eyelids) (OR = 2.49; 95% CI, 1.54–4.03; $p = 1.98E-04$) associated with current prostaglandin analogue use (bimatoprost 0.03%, travoprost 0.005%, or latanoprost 0.004%) versus prostaglandin analogue never or past users. Upper lid ptosis (OR = 4.04; 95% CI, 2.43–6.72; $p = 7.37E-08$), levator dysfunction (OR = 7.51; 95% CI, 3.39–16.65; $p = 6.74E-07$) and lower lid retraction (OR = 2.60; 95% CI, 1.58–4.28; $p = 1.72E-04$) were highly associated with current prostaglandin analogue use versus prostaglandin analogue never or past users.

Table 24 Multivariable odds ratio (95% confidence interval; p-value) for current prostaglandin analogue (PGA) use associated with selected ocular adnexal features

The authors state that these findings are strongly driven by a bimatoprost 0.03% product that is no longer marketed in the United States. Limitations of this study include the inability to recruit sufficient numbers of bimatoprost 0.01% users to perform meaningful analysis, the inability to analyse the reversibility of ocular adnexal changes or find an accurate estimate of the rate for PAP due to the cross-sectional design. However, despite this, the authors consider PAP to be common due to the high odds ratios and significant p-values.

The associations between prostaglandin analogue use and deepening of the upper lid sulci and between prostaglandin analogue use and loss of inferior periorbital fat are confirmed in this multivariable analysis. The associations between prostaglandin analogue use and levator muscle dysfunction and between prostaglandin analogue use and upper lid ptosis represent significant side effects that could impact visual function in glaucoma patients. The authors conclude that latanoprost use produced the least amount of periorbital fat loss but was associated with upper lid ptosis however more studies are needed.

3.1.19 Tan and Berke, 2013 Latanoprost-induced prostaglandin-associated periorbitopathy [33]

This is a small retrospective case series with three cases which reported on cases of latanoprost-induced PAP. The authors note that there have been reports of bimatoprost and travoprost causing deepening of the upper eyelid sulcus, blepharoptosis (drooping of upper eyelid) and enophthalmos however reports involving latanoprost have been less frequent.

This case series discusses three patients, one woman and two men with an average age of 70 years (range 61 to 78 years) who noted eyelid changes on unilateral latanoprost treatment at a routine visit to a glaucoma clinic. The average time period of usage was six years (range three to eight years).

The authors noted that PAP was first associated with bimatoprost and then travoprost. This case series includes photo documentation of PAP in latanoprost users. The authors mention a pharmacologic study compared prostaglandin analogues and it showed that bimatoprost had the strongest effect, followed by travoprost and latanoprost. They also note another study that reported improvement of PAP after switching to latanoprost which indicates the effect of latanoprost is weak.

The authors conclude latanoprost can cause PAP, although it has a lower risk and longer latency of onset than those with bimatoprost and travoprost. Clinicians should be aware of this side effect and monitor for signs periodically. Chronic unilateral prostaglandin use may cause unfavourable asymmetry in the appearance of the periorbital area.

3.1.20 Yoshino et al, 2013 Eyelid and eyelash changes due to prostaglandin analog therapy in unilateral treatment cases [Abstract only] [34]

The purpose of this study was to investigate the incidence of adverse effects on eyelid and eyelashes related to treatment with prostaglandin analogues in patients who apply the medication in only one eye.

39 glaucoma patients who had been treated for over three months continuously in one eye with one of four prostaglandin analogues were included in the study. Face photographs were used to assess adverse effects of prostaglandin analogue treatment on the treated eyes by comparing them with the eyelids and eyelashes of the contralateral eyes. Three examiners calculated scores for the eyelids and eyelashes by counting how many adverse effects were present. There were five possible adverse effects for eyelids and two for eyelashes. A 'positive' finding was when two or more examiners judged that at least one adverse effect was present.

35 (89.7%) patients were judged to have positive eyelid findings and 37 (94.9%) patients were judged to have positive eyelash findings. There was a significant correlation between the period of prostaglandin analogue administration and eyelid score ($P = 0.0218$).

The authors concluded that there was a high incidence of adverse effects caused by prostaglandin analogues in the eyelids and eyelashes. The frequency of adverse effects of the eyelid seemed to increase as the use of prostaglandin analogues was prolonged. The authors stated that cosmetic complications caused by prostaglandin analogue use should be considered and patients should be informed of them in advance.

3.1.21 Arranz-Marquez and Teus, 2007 Effect of age and the development of a latanoprost-induced increase in iris pigmentation [35]

This prospective observational observer-masked study was designed to study the effect of age on the incidence of latanoprost-induced increases in iris pigmentation. The authors state that latanoprost-related iris darkening occurs more frequently during the first six months of therapy, but it is unknown why some people experience changes in iris pigmentation and others do not, so they investigated age as a factor.

72 patients met the inclusion criteria. 36 patients younger than 60 years (group 1) and 36 patients older than 75 years (group 2) with primary open-angle glaucoma participated in this study. Irises of each patient were photographed before and six months after unilateral latanoprost therapy. There were no differences at baseline in the iris colours before latanoprost therapy between the 2 groups.

In the study population, the observers identified 36 cases (50%, $n = 72$) of iris darkening that were considered to have moderate or marked anisochromia after 6 months of latanoprost treatment. There was a significant difference between the groups regarding the relationship between age and the incidence of latanoprost-related iris colour darkening ($P = 0.0001$, chi-square test). Iris darkening was identified in eight patients in group 1 (22.22%, $n = 36$), whereas in group 2 (patients older than 75 years), there were 28 cases of moderate or marked anisochromia (77.78%, $n = 36$; $P = 0.0001$, chi-square test).

The authors conclude that age seems to be an important risk factor for latanoprost-induced iris colour change.

3.1.22 Case reports

3.1.22.1 Joganathan et al, 2021 Prostaglandin analogues: A double-edged sword in orbital glaucoma disease management [36]

This case report looks at the benefits of recognised adverse effects of prostaglandin analogues on periocular structures in patients with unilateral proptosis and intraocular pressure rise. Consideration is given to the intentional use of prostaglandin analogue therapy in this selected cohort of patients with secondary ocular hypertension and proptosis.

The authors present a successfully managed case of secondary OHT combined with unilateral proptosis resulting from idiopathic orbital inflammatory disease (IOID).

A 70-year-old man presented with a one-week history of a painful and red right eye associated with pain on eye movement. The patient had dilated and tortuous episcleral vessels. Computed tomography (CT)

examination of the orbit showed enlarged right medial and inferior rectus muscles. A common cause of extraocular muscle enlargement is thyroid eye disease, and on this assumption, the patient received a total of 1.5 g of intravenous methylprednisolone. However, this did not result in any symptomatic improvement. An orbital biopsy of the right medial rectus revealed chronic inflammation with varying degrees of fibrosis. This was consistent with a diagnosis of IOID, which was promptly treated with oral methotrexate, 7.5 mg a week and folic acid, 5 mg a day. Two weeks later, the patient presented with increasing ocular pain associated with reduction of vision in the right eye and a rise in intraocular pressure. Secondary OHT was diagnosed in the setting of IOID. The patient was started on generic preserved eye drops to the right eye: g. latanoprost at night, g. dorzolamide and g. timolol fixed dose combination twice a day and g. brimonidine twice a day, along with oral slow-release acetazolamide, 250 mg, twice daily. This combination reduced the intraocular pressure to 20 mmHg over the following two weeks. The patient subsequently developed preservative-related corneal punctate keratopathy and secondary drop intolerance. He was therefore switched to the preservative-free drop equivalents of latanoprost and dorzolamide and timolol fixed combination, which resulted in good intraocular pressure control as well a marked improvement in ocular surface signs and symptoms.

The authors conclude that prostaglandin analogues can act as a double-edged sword in the management of raised intraocular pressure by reducing eye pressure at the cost of developing adverse effects of PAP. These adverse effects, however, can be beneficial in the aesthetic rehabilitation of proptosis and associated keratopathy in patients with unilateral orbital disease.

3.1.22.2 Yip and Ramasamy, 2018 Case report: Unilateral orbital fat change [37]

A 65-year-old man attended a routine glaucoma follow-up complaining that his left eye had changed in appearance. He had been taking bimatoprost for glaucoma for over four years in his left eye only. Extensive loss of orbital fat giving the appearance of a sunken in globe was noted and a diagnosis of prostaglandin-associated periorbitopathy was made. The authors conclude that although this is a side effect in patients taking a prostaglandin analogue, non-ophthalmology clinicians may not encounter many of these patients in routine practice and should therefore be aware of this possible side effect.

3.1.22.3 Fong et al, 2016 Audible blink in prostaglandin-associated periorbitopathy [15]

Fong et al reported on a single person case report concerning a 72 year old woman who presented with a one year history of audible clicking sounds when blinking [15]. The patient had been taking bimatoprost for three years followed by travoprost for two years for glaucoma. The authors named this 'blepharothorevia' and consider it to be added to the growing list of features of PAP. The authors note that PAP can be partially reversed by prostaglandin agonist treatment cessation however it is not known whether blepharothorevia would completely resolved with medication cessation [15].

3.1.22.4 Shrirao et al, 2016 Prostaglandin-associated periorbitopathy [38]

This reports on a 59-year-old man on topical bimatoprost for primary open-angle glaucoma in the left eye. He had been using bimatoprost for the six years. The man presented with deepening of superior sulcus, periorbital fat atrophy, mild ptosis and 2 mm of enophthalmos in his left eye, which are typically seen in PAP.

These authors note that PAP, first reported in 2004, has been reported with the use of bimatoprost, travoprost, tafluprost and latanoprost.

3.1.22.5 Yang et al, 2009 Deepening of eyelid superior sulcus during topical travoprost treatment [39]

This is a case report of one patient with unilateral normal-tension glaucoma and another patient with unilateral primary open-angle glaucoma. Both patients were treated with travoprost monotherapy unilaterally for two years.

The authors note that topical travoprost has several known side effects including a darkening of the eyelid and eyelash hypertrichosis, but at the time of the report there had been no reports of a deepening of the eyelid superior sulcus associated with its use.

The first case is a 66-year-old Korean woman who started once daily travoprost treatment in her right eye. Two years later she noticed a sunken appearance of the right eyelid. On examination she had a deepening of the eyelid superior sulcus of the right eye and a clinically significant disparity between the two eyes was apparent. The patient was happy to continue with treatment and 12 months later the deepening of the eyelid superior sulcus was not altered.

The second case is a 67-year-old Korean man who started travoprost treatment in his left eye. At his two year follow up visit he complained of marked eyelid differences and a sunken appearance and darkening of the left eyelid. The patient decided to change treatment to dorzolamide and timolol combination solution was substituted for travoprost. After six months, hyperpigmentation and hypertrichosis of the upper eyelid had slight decreased but the eyelid superior sulcus deepening did not change. Fifteen months after discontinuation of travoprost the sulcus deepening had much improved in the left eye.

Both patients in this case report gradually developed a deepening of the eyelid superior sulcus with hyperpigmentation in the eyelid skin of the treated eye. The differences between the treated and untreated eyes were quite visible however the differences returned to normal after discontinuation of travoprost for 15 months.

A limitation of the study is that photographs were not obtained before starting travoprost treatment. Patients were certain about eye changes however and a disparity between the eyes is apparent in photographs during treatment.

The authors concluded that a deepening of the eyelid sulcus should be considered a possible complication of topical travoprost that can be reversed by discontinuation of the medication.

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]



3.3 CARM data

Medsafe has not been made aware of any cases of prostaglandin associated periorbitopathy reported in New Zealand in association with either bimatoprost, latanoprost or travoprost.

CARM have received four reports for bimatoprost, 28 reports for latanoprost and six reports for travoprost associated with an eye related disorder however none appear to relate to PAP.

4 DISCUSSION AND CONCLUSIONS

This report has summarised information relating to prostaglandin analogues and PAP. Prostaglandin analogues, such as bimatoprost, latanoprost and travoprost, lower intraocular pressure in the treatment of glaucoma. However, they have also been associated with causing PAP, which is a term used to describe a number of clinical and cosmetic symptoms. Following a review, product information has been updated in the United Kingdom to include PAP as an adverse reaction for bimatoprost-containing medicines. This paper aims to determine whether PAP is a class effect and whether the risk differs across the class.

The New Zealand data sheets for prostaglandin analogues do not currently list PAP as an adverse reaction. They all include clinical characteristics of PAP however the exact terms vary between data sheets.

Medsafe notes UK and European product information for bimatoprost-containing medicines has been updated with wording regarding the risk of PAP. Medsafe recommends that data sheets for products containing bimatoprost in New Zealand should also be updated with similar wording to address the risk of PAP.

Many studies note the usefulness of prostaglandin analogues in the treatment of glaucoma. However, many authors also mention the importance of clinicians being aware of PAP and informing patients of the possible ocular effects of their glaucoma treatment before starting treatment, especially in unilateral administration.

A recent proposed mechanism suggests that PAP is thought to be caused by orbital fat atrophy from inhibition of adipogenesis through FP receptor stimulation.

Overall, the studies appear to suggest that all prostaglandin analogues have the potential to cause PAP. PAP may be more severe and/or occur more frequently with bimatoprost than travoprost and latanoprost. PAP also appears to be at least partially reversible.

5 ADVICE SOUGHT

The Committee is asked to advise:

- whether the risk of prostaglandin associated periorbitopathy is a class effect
- if yes, whether the risk differs across the class
- whether any communication, other than MARCs Remarks is required.

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