

Greater East Midlands Commissioning Support Unit in association with  
Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services,  
United Lincolnshire Hospitals Trust and Lincolnshire Partnership Foundation Trust

# Lincolnshire Prescribing and Clinical Effectiveness Bulletin

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## PRESCRIBING FOR CHRONIC OPEN ANGLE GLAUCOMA (COAG) AND OCULAR HYPERTENSION (OHT)

### Key Points

- This review of existing guidance has been necessitated by the introduction of lower cost generic preparations and new products and the discontinuation of some existing product lines.
- Treatment for COAG and OHT should be initiated by a secondary care based ophthalmologist, although ongoing prescribing may be undertaken by a GP or non-medical prescriber. As a result of this, all of the products recommended for use are designated AMBER without shared care.
- Wherever possible, eye preparations should be prescribed as multi-dose containers. Preservative free formulations are considerably more expensive than multi-dose equivalents and should be reserved for use in patients with genuine cases of hypersensitivity to the preservative or following corneal transplant surgery.

### Prostaglandin analogue eye preparations (PGAs): first line for patients newly diagnosed with mild to moderate COAG.

- NICE recommend that all people newly diagnosed with early or moderate chronic open angle glaucoma (COAG) and at risk of significant visual loss in their lifetime should be offered a prostaglandin analogue (PGA) eye preparation.
- A recently published meta-analysis has concluded that bimatoprost, latanoprost and travoprost produce similar reductions in intra-ocular pressure (IOP), although there is some variation in the incidence of key adverse reactions.
- Lower cost generic latanoprost 50mcg per ml eye drops (2.5ml bottle) are the preferred first line option in people with glaucoma or raised intraocular pressure (IOP), particularly in those with early, mild disease. Prescribers are urged to ensure that all prescribing of latanoprost 50mcg per ml eye drops is generic. At present, brand name prescribing of *Xalatan* 50mcg per ml eye drops is causing an unnecessary additional cost across Lincolnshire of £36,700pa (see text for individual CCG figures).
- Second line options for those who have failed to achieve the desired reduction in IOP with latanoprost or who are unable to tolerate the product are either travoprost 40microgram per ml (*Travatan*) or third line for new patients bimatoprost 100mcg per ml (*Lumigan*).

- In view of the imminent discontinuation of bimatoprost 300mcg per ml eye drops (*Lumigan*), prescribers are encouraged to identify all patients currently using this strength with a view to switching them to bimatoprost 100mcg per ml eye drops (*Lumigan*). The manufacturer, Allergan, has produced published evidence confirming equivalent effectiveness between the two strengths. The licensed dose of bimatoprost 100mcg per ml eye drops (*Lumigan*) is one drop daily into the affected eye. Bimatoprost 300mcg per ml eye drops (*Lumigan*) have been removed from the *Lincolnshire Joint Formulary* and replaced by the 100mcg per ml strength; designation AMBER without shared care. The higher price of the 100mcg per ml strength will increase Lincolnshire prescribing costs by £38,700 (see text for individual CCG impact).
- Where a preservative-free preparation is indicated, latanoprost 50mcg per ml (*Monoprost*) should be preferred; designation AMBER without shared care. Both preservative-free bimatoprost 300mcg per ml drops (*Lumigan*) and preservative-free tafluprost 15mcg per ml drops (*Saflutan*) are also included in the *Lincolnshire Joint Formulary* and designated AMBER without shared care to enable flexibility in patients insufficiently responsive to or intolerant of latanoprost.

## Second line alternatives

### (1) Beta-blockers

- For early to moderate COAG, NICE recommend that PGAs should be considered first line; if the target reduction in IOP is not achieved with the first PGA, a second should be considered or PGA/beta-blocker (BB) combination therapy. If the target IOP is still not achieved, PGA/BB/carbonic anhydrase inhibitor combination therapy should be considered.
- Generic timolol 0.25% and 0.5% eye drops are approved as the first line BBs of choice; both products are designated AMBER without shared care.
- Betaxolol 0.25% and 0.5% eye drops (*Betoptic*) and levobunolol 0.5% eye drops (generic/*Betagan*) are approved as second line alternatives to timolol and are also designated AMBER without shared care.
- Where a once daily timolol eye preparation is indicated, timolol 0.25% and 0.5% gel forming solution (*Timoptol-LA*) is approved as AMBER without shared care.
- Preservative-free single-dose preparations of timolol, betaxolol and levobunolol are also approved for use in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery; designation AMBER without shared care (see text).

### (2) Prostaglandin analogue/beta-blocker combination products

- Bimatoprost 300mcg/ timolol 5mg per ml eye drops (*Ganfort*), latanoprost 50mcg/ timolol 5mg per ml eye drops (generic) and travoprost 40mcg/ timolol 5mg per ml drops (*DuoTrav*) are all approved for use on the *Lincolnshire Joint Formulary*; designation AMBER without shared care. Latanoprost 50mcg/ timolol 5mg per ml eye drops should always be prescribed generically, not as *Xalacom*. Where a combination PGA/BB preparation is indicated, local ophthalmologists prefer bimatoprost 300mcg/ timolol 5mg per ml eye drops (*Ganfort*) and travoprost 40mcg/ timolol 5mg per ml drops (*DuoTrav*).
- Combination PGA/BB preparations should usually be administered in the evening. When adding a BB to a PGA, select the combination product containing the same PGA as previously prescribed as monotherapy unless this was not tolerated.

**(3) Carbonic anhydrase inhibitors (CAIs)**

- Dorzolamide 2% eye drops are now available generically at a significantly lower cost than either branded Trusopt or brinzolamide 1% eye drops (Azopt). However, as dorzolamide 2% eye drops are formulated at a lower pH than brinzolamide, they can be more irritant to the eye causing an unpleasant stinging sensation on application. As a result of this, despite the lower cost of generic dorzolamide, both products are approved for inclusion in the *Lincolnshire Joint Formulary* as possible first line options; designation AMBER without shared care. Prescribers should ensure that all remaining prescriptions for the *Trusopt* brand of dorzolamide 2% eye drops are genericised.
- The single dose preservative-free formulation of dorzolamide (*Trusopt*) should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery.

**(4) Carbonic anhydrase inhibitor/beta blocker combinations**

- When adding a BB to a CAI, select the combination product containing the same CAI as previously received as monotherapy unless this was not tolerated.
- The emergence of lower cost generic dorzolamide 2% eye drops and dorzolamide 2%/timolol 0.5% eye drops means that dorzolamide containing preparations should be considered as first line alternatives to brinzolamide 1% eye drops (Azopt) and brinzolamide 1%/timolol 0.5% eye drops (*Azarga*). Both dorzolamide 2%/timolol 0.5% drops (generic) and brinzolamide 1%/timolol 0.5% drops (*Azarga*) are approved for use through the *Lincolnshire Joint Formulary* and designated AMBER without shared care. Prescribers should ensure that all remaining prescriptions for the *Cosopt* brand of dorzolamide 2%/timolol 0.5% eye drops are genericised.
- The single dose preservative free formulation of *Cosopt* is also designated AMBER without shared care, but should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery.

**(5) Alpha 2 agonists**

- Local ophthalmologist advice is that alpha 2 agonists should be considered as primary treatment for those patients who are non-responders or are allergic to both PGAs and CAIs. They should also be considered as a third medication for patients who have partly responded to treatments with PGAs and CAIs but who decline surgery or in whom surgery is contraindicated.
- Generic brimonidine 0.2% eye drops are the preferred alpha 2 agonist eye preparation and are designated AMBER without shared care. Prescribers should ensure that all remaining prescriptions for the *Alphagan* brand of brimonidine 0.2% eye drops are genericised.
- Apraclonidine 0.5% solution (*Iopidine*) is also designated AMBER without shared care, but should only be used short-term (a maximum of one month) as an adjunctive treatment of chronic glaucoma to delay laser treatment or glaucoma surgery in patients not adequately controlled with other treatments.

**(6) Carbonic anhydrase inhibitors/ alpha 2 agonist combination products**

- The new carbonic anhydrase inhibitor/ alpha 2 agonist combination product *Simbrinza* eye drops (Brinzolamide 1%/brimonidine 0.2%) should only be used for those patients unable to tolerate alternative combination therapies such as PGA/BBs or CAI/BBs.

### **(7) Alpha 2 agonists/ beta-blocker combination**

The alpha 2 agonist/BB combination preparation *Combigan* should only be used for those patients unable to tolerate prostaglandin analogues and carbonic anhydrase inhibitors when treatment with a beta-blocker alone is not adequate. Brimonidine 0.2%/timolol 0.5% eye drops (*Combigan*) is designated AMBER without shared care.

### **(8) Systemic treatments (oral carbonic anhydrase inhibitors)**

- Acetazolamide 250mg tablets (*Diamox*) and sustained release capsules (*Diamox SR*) are recommended for short term use only as an adjunct to other treatments in people with raised IOP. Oral carbonic anhydrase inhibitors are not recommended for long term use as they can cause agranulocytosis, thrombocytopenia, electrolyte disturbances and metabolic acidosis. Regular monitoring of full blood count and plasma electrolyte count is recommended. Both products are designated AMBER without shared care for this indication.

## **SUMMARY OF PACEF DECISIONS: MARCH 2015**

### **Prostaglandin analogue eye preparations (PGAs): first line for patients newly diagnosed with mild to moderate COAG.**

<b>Drug</b>	<b>Indication(s)</b>	<b>Traffic Light Status</b>
<b>First Line</b>		
Latanoprost 50mcg per ml drops (generic) (2.5ml bottle)	COAG and OHT	AMBER without shared care 1st line for those with early or mild disease.
<b>Second Line</b>		
Bimatoprost 100mcg/ml eye drops ( <i>Lumigan</i> ) (3ml bottle)	COAG and OHT	AMBER without shared care 2nd line for those who have failed to achieve the desired reduction in IOP with latanoprost or who cannot tolerate latanoprost
Travoprost 40mcg per ml drops ( <i>Travatan</i> ) (2.5ml bottle)	OHT and COAG	AMBER without shared care 2nd line for those who have failed to achieve the desired reduction in IOP with latanoprost or who cannot tolerate latanoprost

### **Second line alternatives**

#### **Beta-blockers**

<b>Beta Blocker Eye Preparations</b>		
<b>First Line</b>		
Timolol 0.25% and 0.5% eye drops (generic) (5ml bottle)	OHT, COAG and secondary glaucoma	AMBER without shared care 1st line BB eye preparation of choice.
<i>Timoptol LA</i> 0.25% and 0.5% gel forming eye drops (2.5ml bottle)	OHT, COAG and secondary glaucoma	Amber without shared care Once daily multi-dose preparation
<b>Second Line</b>		
Betaxolol 0.25% and 0.5% eye drops ( <i>Betoptic</i> ) (5ml bottle)	OHT and COAG	AMBER without shared care Second line BB after timolol eye drops
Levobunolol 0.5% eye drops (generic/ <i>Betagan</i> ) (5ml bottle)	OHT and COAG	AMBER without shared care Second line BB after timolol eye drops

### **Prostaglandin analogue/beta-blocker combination products**

<b>Drug</b>	<b>Indication(s)</b>	<b>Traffic Light Status</b>
Latanoprost 0.005%/ timolol 0.5% eye drops (generic)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	AMBER without shared care. Prescribe generically and not as the higher cost branded preparation <i>Xalacom</i> .

Bimatoprost 300mcg/ timolol 5mg per ml eye drops ( <i>Ganfort</i> ) (3ml bottle)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	AMBER without shared care
Travoprost 40mcg/ timolol 5mg per ml drops ( <i>DuoTrav</i> ) (2.5ml bottle)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	AMBER without shared care

### **Carbonic anhydrase inhibitors**

<b>Drug</b>	<b>Indication(s)</b>	<b>Traffic Light Status</b>
Brinzolamide 1% drops ( <i>Azopt</i> ) (5ml bottle)	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in COAG or OHT	AMBER without shared care
Dorzolamide 2% eye drops (generic)	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in OHT, COAG or pseudo-exfoliative glaucoma	AMBER without shared care Prescribe generically and not as the higher cost branded preparation <i>Trusopt</i> .

### **Carbonic anhydrase inhibitors/beta-blocker combination products**

<b>Drug</b>	<b>Indication(s)</b>	<b>Traffic Light Status</b>
Brinzolamide 1%/ timolol 0.5% eye drops ( <i>Azarga</i> )	Raised intraocular pressure in COAG or OHT where monotherapy is inadequate	AMBER without shared care
Dorzolamide 2%/ timolol 0.5% eye drops (generic)	Raised intraocular pressure in COAG or OHT where monotherapy is inadequate	AMBER without shared care Prescribe generically and not as the higher cost branded preparation <i>Cosopt</i> .

### **Alpha 2 agonists**

<b>Drug</b>	<b>Indication(s)</b>	<b>Traffic Light Status</b>
Brimonidine 0.2% eye drops (generic)	COAG or OHT as monotherapy where BBs are contraindicated or as adjunct to other agents when target IOP is not achieved with a single agent	AMBER without shared care Alpha 2 agonist eye preparation of choice
Apraclonidine 0.5% solution ( <i>Iopidine</i> )	Short-term adjunctive treatment of chronic glaucoma to delay laser treatment or glaucoma surgery	AMBER without shared care Should only be used short-term (a maximum of one month) as an adjunctive treatment of chronic glaucoma to delay laser treatment or glaucoma surgery in patients not adequately controlled with other treatments.

### **Carbonic anhydrase inhibitors/ alpha 2 agonist combination products**

<b>Drug</b>	<b>Indication(s)</b>	<b>Traffic Light Status</b>
Brinzolamide 10mg/brimonidine 2mg ( <i>Simbrinza</i> )	Reduction in IOP in COAG or OHT insufficiently responsive to monotherapy	AMBER without shared care Should only be used for those patients unable to tolerate alternative combination therapies such as prostaglandin analogues/ beta-blockers or carbonic anhydrase inhibitors/ beta blockers.

### **Alpha 2 agonists/ beta-blocker combination**

<b>Drug</b>	<b>Indication(s)</b>	<b>Traffic Light Status</b>
Brimonidine 0.2%/timolol 0.5% eye drops ( <i>Combigan</i> )	Reduction in IOP in COAG or OHT insufficiently responsive to topical BBs	AMBER without shared care. Should only be used for those unable to tolerate PGAs and CAIs when treatment with a BB alone is not adequate.

### **Systemic treatments (oral carbonic anhydrase inhibitors)**

<b>Drug</b>	<b>Indication(s)</b>	<b>Traffic Light Status</b>
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Acetazolamide tablets 250mg ( <i>Diamox</i> )	Reduction of IOP in COAG, secondary glaucoma and peri-operatively in angle closure glaucoma	AMBER without shared care. For short term use only as an adjunct to other treatments in people with raised IOP.
Acetazolamide capsules MR 250mg ( <i>Diamox SR</i> )	Reduction of IOP in COAG, secondary glaucoma and peri-operatively in angle closure glaucoma	AMBER without shared care. For short term use only as an adjunct to other treatments in people with raised IOP.

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## Introduction

In May 2010 PACEF issued guidance on the treatment of chronic open angle glaucoma (COAG) and ocular hypertension (OHT) (see *PACE Bulletin* Vol 4 No 6 (May 2010)). Many of the recommendations were drawn from NICE Clinical Guideline 85, *Glaucoma: Diagnosis and management of chronic open angle glaucoma and ocular hypertension* (April 2009). This guidance has now been reviewed and updated in collaboration with ophthalmologists from United Lincolnshire Hospitals. The review was necessitated by the introduction of lower cost generic preparations and new products and the discontinuation of some existing product lines.

## General principles

- Treatment for COAG and OHT should be initiated by a secondary care based ophthalmologist, although ongoing prescribing may be undertaken by a GP or non-medical prescriber. As a result of this, all of the products recommended for use are designated AMBER without shared care.
- Wherever possible, eye preparations should be prescribed as multi-dose containers. Preservative free formulations are considerably more expensive than multi-dose equivalents and should be reserved for use in patients with genuine cases of hypersensitivity to the preservative or following corneal transplant surgery.

## First line treatments: Prostaglandin analogues (PGAs)

**NICE recommend that all people newly diagnosed with early or moderate chronic open angle glaucoma (COAG) and at risk of significant visual loss in their lifetime should be offered a prostaglandin analogue (PGA) eye preparation (see NICE Clinical Guideline 85).** The currently available products including licensed indications, doses and comparative costs are tabulated below:

Prostaglandin analogue	Licensed indications	Recommended dose	Cost
Bimatoprost 0.1mg per ml drops ( <i>Lumigan</i> )	As monotherapy or as an adjunct to BBs in COAG or OHT	One drop into the affected eye once daily in the evening	3ml £11.71
Bimatoprost 0.3mg per ml	As monotherapy or as	One drop into the	3ml £10.30

drops ( <i>Lumigan</i> )	an adjunct to BBs in COAG or OHT	affected eye once daily in the evening	Discontinued
Bimatoprost 0.3mg per ml drops (preservative-free; single dose)	As monotherapy or as an adjunct to BBs in COAG or OHT	One drop into the affected eye once daily in the evening	£13.75 (30)
Latanoprost 50mcg per ml drops (generic)	COAG and OHT	One drop into the affected eye once daily in the evening	2.5ml £2.00
Latanoprost 50mcg per ml drops ( <i>Xalatan</i> )	COAG and OHT	One drop into the affected eye once daily in the evening	2.5ml £12.48
Latanoprost 50mcg/ml drops ( <i>Monopost</i> ) (preservative-free; single dose)	COAG and OHT	One drop into the affected eye once daily in the evening	£8.49 (30) £25.47 (90)
Tafluprost 15mcg per ml drops ( <i>Saflutan</i> ) (preservative-free; single dose)	As monotherapy or as an adjunct to BBs in COAG or OHT	One drop into the affected eye once daily in the evening	£12.20 (30)
Travoprost 40mcg per ml drops ( <i>Travatan</i> )	OHT and COAG	One drop into the affected eye once daily in the evening	2.5ml £10.95

Latanoprost, tafluprost and travoprost are all PGAs; bimatoprost is a prostamide analogue. All of these agents work by increasing uveoscleral outflow resulting in reductions in intraocular pressure (IOP) of between 25 and 35%.

PGAs can cause darkening of the iris in 5 to 20% of patients. As a result of this, **PGA treatment should normally be reserved for those receiving treatment for both eyes.** Where unocular use is being considered, the patient should be informed of this risk and consent to treatment recorded in their medical notes. If only one eye is affected, alternative first-line treatments include either a carbonic anhydrase inhibitor or, if there are no contraindications, a beta-blocker (see below).

In addition, all PGAs can also cause conjunctival hyperaemia (red eye) and hypertrichosis of the eyelashes (prolific growth). Patients receiving treatment with PGAs should be monitored for any changes to growth of lashes and eye colouration.

PGAs should not be used in women of child bearing potential unless adequate contraceptive measures are in place. If PGAs need to be used in pregnancy, the prescriber should ensure that the patient is fully informed of the potential risks if they become pregnant. Such patients should be advised to seek advice from either their GP or ophthalmologist if they decide to discontinue contraceptive use or if they suspect they have become pregnant.

A recently published meta-analysis has concluded that bimatoprost, latanoprost and travoprost produce similar reductions in IOP, although there is some variation in the incidence of key adverse reactions.

### **Generic latanoprost 50mcg per ml drops**

Latanoprost 50mcg per ml drops are now available as a generic preparation and emerge from the cost comparison as significantly lower in price than any of the alternative PGAs.

#### **PACEF Recommendation:**

**Lower cost generic latanoprost 50mcg per ml eye drops (2.5ml bottle) are the preferred first line option in people with glaucoma or raised intraocular pressure (IOP), particularly in those with early, mild disease. Prescribers are urged to ensure**

that all prescribing of latanoprost 50mcg per ml eye drops is generic. At present, brand name prescribing of *Xalatan* 50mcg per ml eye drops is causing an unnecessary additional cost across Lincolnshire of £36,700pa (LECCG £6,539, LWCCG £16,936, SLCCG £6,581 and SWLCCG £6,707).

**PACEF Recommendation:**

Second line options for those who have failed to achieve the desired reduction in IOP with latanoprost or who are unable to tolerate the product are either travoprost 40mcg per ml (*Travatan*) or third line for new patients bimatoprost 100mcg per ml (*Lumigan*).

***Discontinuation of bimatoprost 300mcg per ml drops (Lumigan)***

Allergan have recently announced their intention to discontinue bimatoprost 300mcg per ml drops multidose eye drops (*Lumigan*) by the end of April 2015. Patients currently receiving bimatoprost 300mcg/ml multidose eye drops will need to be switched to an alternative product. In the absence of a directly equivalent preparation, this will necessitate the switching of patients to the lower strength bimatoprost 100mcg per ml drops. **The recommended dose should be one drop daily.**

Allergan have stated that there is published evidence confirming comparable effectiveness between the 100mcg/ml and 300mcg/ml strengths of *Lumigan*. PACEF reviewed a non-inferiority study five years ago when the lower strength product was first launched. This study compared the efficacy and adverse effects of three strengths of bimatoprost 100mcg/ml, 125mcg/ml (unlicensed) and 300mcg/ml (see *PACE Bulletin* Vol 4 No 14). In addition to comparable efficacy, a lower incidence of side effects was reported with the lower strength. When evaluating this study, PACEF were concerned about the differences in efficacy between the three strengths and were particularly concerned that an intermediate strength (125mcg/ml) appeared to be less effective than both the 100mcg/ml and the 300mcg/ml. These concerns, in addition to the higher cost of the 100mcg/ml strength resulted in bimatoprost 100mcg per ml drops (*Lumigan*) being initially designated RED/RED. The discontinuation of the 300mcg/ml strength has led to this decision being over-turned and bimatoprost 100mcg/ml eye drops (*Lumigan*) are now designated AMBER without shared care.

The ULHT ophthalmology service has confirmed that the majority of patients currently receiving treatment with bimatoprost 300mcg per ml eye drops will have already received treatment with at least one other PGA (either latanoprost or travoprost). This means that, when bimatoprost 300mcg per ml eye drops are withdrawn, bimatoprost 100mcg per ml eye drops will be the most appropriate alternative for most patients.

There is a difference in the concentration of the preservative benzalkonium chloride (BAC) between the higher and lower strengths of bimatoprost. Bimatoprost 100mcg/ml contains 0.2mg/ml BAC (the same concentration as that found in latanoprost formulations) whereas the higher strength product had a lower concentration of BAC, 0.05mg/ml. If patients do not tolerate the preservative content of the eye drop, standard advice is to consider a preservative-free product.

**PACEF Recommendation:**

In view of the discontinuation of bimatoprost 300mcg per ml eye drops (*Lumigan*), prescribers are encouraged to identify all patients currently using this strength with a view to switching them to bimatoprost 100mcg per ml eye drops (*Lumigan*). The licensed dose of bimatoprost 100mcg/ml is one drop daily into each affected eye. Bimatoprost 300mcg per ml eye drops (*Lumigan*) are to be removed from the *Lincolnshire Joint Formulary* and replaced by the 100mcg per ml strength;

designation AMBER without shared care. The higher price of the 100mcg per ml strength will increase Lincolnshire prescribing costs by £38,700 (LECCG £15,488, LWCCG £5,674, SLCCG £13,187 and SWLCCG £4,354).

### **Preservative- free formulations (single use only)**

<b>Prostaglandin analogue</b>	<b>Licensed indications</b>	<b>Recommended dose</b>	<b>Cost</b>
Bimatoprost 300mcg per ml drops ( <i>Lumigan</i> ) (preservative-free; single dose)	As monotherapy or as an adjunct to BBs in COAG or OHT	One drop into the affected eye once daily in the evening	£13.75 (30)
Latanoprost 50mcg/ml drops ( <i>Monoprost</i> ) (preservative-free; single dose)	COAG and OHT	One drop into the affected eye once daily in the evening	£8.49 (30) £25.47 (90)
Tafluprost 15mcg per ml drops ( <i>Saflutan</i> ) (preservative-free; single dose)	As monotherapy or as an adjunct to BBs in COAG or OHT	One drop into the affected eye once daily in the evening	£12.20 (30)

### **PACEF Recommendations**

Preservative free formulations should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery. Whilst, the preservative-free formulation of latanoprost 50mcg per ml eye drops (*Monoprost*) is considerably more expensive than generic latanoprost 50mcg per ml eye drops it is less costly than the multi-dose formulations of bimatoprost 100mcg per ml and travoprost 15mcg per ml (see table above). Where a preservative-free preparation is indicated, latanoprost 50mcg per ml (*Monoprost*) should be preferred; designation AMBER without shared care. Both preservative-free bimatoprost 300mcg per ml drops (*Lumigan*) and preservative-free tafluprost 15mcg per ml drops (*Saflutan*) are also included in the *Lincolnshire Joint Formulary* and designated AMBER without shared care to enable flexibility in patients insufficiently responsive to or intolerant of latanoprost.

### **Second line treatments**

For early to moderate COAG, NICE recommend that PGAs should be considered first line; if the target reduction in IOP is not achieved with the first PGA, a second should be considered or PGA/beta-blocker (BB) combination therapy. If the target IOP is still not achieved, PGA/BB/carbonic anhydrase inhibitor combination therapy should be considered.

#### (1) Beta-blockers (BBs)

BBs should be used in accordance with the NICE Clinical Guidelines as outlined above. In newly diagnosed cases of early or moderate COAG where only one eye is affected, a BB (if there are no contraindications) or a carbonic anhydrase inhibitor should be considered as first line alternatives. The currently available products, licensed indications, doses and comparative costs are tabulated below:

<b>Beta-Blockers</b>	<b>Licensed indications</b>	<b>Recommended dose</b>	<b>Cost</b>
Betaxolol 0.25% eye drop suspension ( <i>Betoptic Suspension</i> )	OHT and COAG	One drop into the affected eye twice a day	5ml £2.66
Betaxolol 0.5% eye drops ( <i>Betoptic Solution</i> )	OHT and COAG	One drop into the affected eye twice a day	5ml £1.90
Betaxolol 0.25%	OHT and COAG	One drop into the	50 x 0.25ml £13.77

suspension single dose vials preservative-free ( <i>Betoptic Suspension</i> )		affected eye twice a day	
Carteolol 1% eye drops ( <i>Teoptic</i> )	OHT, COAG and some secondary glaucomas	One drop into the affected eye twice a day	5ml £7.60
Carteolol 2% eye drops ( <i>Teoptic</i> )	OHT, COAG and some secondary glaucomas	One drop into the affected eye twice a day	5ml £8.40
Levobunolol 0.5% drops (generic)	COAG and OHT	One drop into the affected eye once or twice daily	5ml £1.85
Levobunolol 0.5% drops ( <i>Betagan</i> )	COAG and OHT	One drop into the affected eye once or twice daily	5ml £1.85
Levobunolol 0.5% preservative-free single-use eye drops ( <i>Betagan</i> )	COAG and OHT	One drop into the affected eye once or twice daily	30 x 0.4ml £9.98
Timolol 0.25% eye drops (generic)	OHT, COAG and secondary glaucoma	One drop into the affected eye twice daily	5ml £1.40
Timolol 0.5% eye drops (generic)	OHT, COAG and secondary glaucoma	One drop into the affected eye twice daily	5ml £1.32
Timolol 0.25% eye drops ( <i>Timoptol</i> )	OHT, COAG and secondary glaucoma	One drop into the affected eye twice daily	5ml £3.12
Timolol 0.25% solution in preservative-free unit dose vials ( <i>Timoptol</i> )	OHT, COAG and secondary glaucoma	One drop into the affected eye twice daily	30 x 0.2ml £8.45
Timolol 0.5% eye drops ( <i>Timoptol</i> )	OHT, COAG and secondary glaucoma	One drop into the affected eye twice daily	5ml £3.12
Timolol 0.5% solution in preservative-free unit dose vials ( <i>Timoptol</i> )	OHT, COAG and secondary glaucoma	One drop into the affected eye twice daily	30 x 0.2ml £9.65
Timolol 0.25% gel-forming eye drops ( <i>Timoptol LA</i> )	OHT, COAG and secondary glaucoma	One drop into the affected eye once daily	2.5ml £3.12
Timolol 0.5% gel-forming eye drops ( <i>Timoptol LA</i> )	OHT, COAG and secondary glaucoma	One drop into the affected eye once daily	2.5ml £3.12
Timolol 0.1% preservative-free single use ophthalmic gel ( <i>Tiopex</i> )	OHT and COAG	One drop in the affected eye(s) daily, preferably in the morning	30 x 0.4g £7.49

BB eye drop formulations reduce IOP by approximately 25%. BBs are contra-indicated in bradycardia, heart block or uncontrolled heart failure. The Committee on Safety of Medicines has advised that BBs, even those with apparent cardio-selectivity, should not be used in patients with asthma or a history of obstructive airways disease, unless no alternative treatment is available. In such cases, appropriate precautions should be taken to reduce the risk of inducing bronchospasm. Betaxolol is more cardioselective than timolol, but seems to be less effective.

#### **PACEF Recommendations**

**Generic timolol 0.25% and 0.5% eye drops are approved as the first line BBs of choice; both products are designated AMBER without shared care. Timolol 0.25% and 0.5% solution in preservative-free unit dose vials (*Timoptol*) is also designated AMBER without shared care, but should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery. Betaxolol 0.25% and 0.5% eye drops (*Betoptic*) and levobunolol 0.5% eye drops (generic/*Betagan*) are approved as second line alternatives to timolol and are designated AMBER without shared care. Preservative free betaxolol 0.25% suspension (*Betoptic*) and levobunolol 0.5% preservative-free single-use eye drops**

**(Betagan)** are also approved as AMBER without shared care in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery. Where a once daily timolol eye preparation is indicated, timolol 0.25% and 0.5% gel forming solution (*Timoptol-LA*) is approved as AMBER without shared care; a timolol 0.1% preservative free gel (*Tiopex*) is also approved in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery, designated AMBER without shared care. Carteolol 1% and 2% eye drops (*Teoptic*) are prohibitively expensive and should not be prescribed; designation RED-RED.

## **(2) Prostaglandin analogue/beta-blocker combination products**

Combination preparations can help to improve adherence by reducing the number of preparations and doses.

<b>PGA/BB combination</b>	<b>Indication(s)</b>	<b>Recommended dose</b>	<b>Cost</b>
Bimatoprost 300mcg/ timolol 5mg per ml eye drops ( <i>Ganfort</i> ) (3ml bottle)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	One drop into the affected eye once daily in the morning or evening	3ml £13.95 3 x 3ml £37.59
Latanoprost 50mcg/ timolol 5mg per ml eye drops (generic)	OHT and COAG insufficiently responsive to topical BBs or prostaglandin analogues	One drop into the affected eye once daily	2.5ml £3.87
Latanoprost 50mcg/ timolol 5mg per ml eye drops ( <i>Xalacom</i> )	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	One drop into the affected eye once daily	2.5ml £14.32 3 x 2.5ml £39.68
Travoprost 40mcg/ timolol 5mg per ml drops ( <i>DuoTrav</i> )	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	One drop into the affected eye once daily in the morning or evening	2.5ml £13.95 Patent expiry: August 2014.

Unless otherwise stated, combination PGA and BB preparations should be administered in the evening. When adding a BB to a PGA, select the combination product containing the same PGA as previously prescribed as monotherapy unless this was not tolerated.

In line with formulary recommendations for the use of prostaglandin analogues and beta blockers, preparations containing latanoprost, bimatoprost and travoprost in combination with timolol are all included on the *Joint Formulary*, designated AMBER without shared care.

Based on limited evidence from a small (n=195) single study, it is possible that the use of latanoprost and timolol in a combination preparation is not as effective as using the two components prescribed separately. A 12 week randomised multi-centered study published in the *British Journal of Ophthalmology* in 2004 compared the IOP lowering effect and safety of a fixed dose once daily latanoprost and timolol combination with the concomitant use of the individual components. Results showed that after 12 weeks there was a difference in mean diurnal IOP levels between the fixed combination and the separate components of 1.1mmHg, favouring the separate components. The primary endpoint of the study of non-inferiority of the combination product compared to the individual components was not reached. It is possible that this can be explained by the fact that patients on the fixed dose combination administered their dose in the morning, whereas those on the separate components administered the latanoprost component in the evening. Previous published evidence has suggested that latanoprost is more effective if administered in the evening. It is also possible that patient's benefited from the additional dose of timolol in separate component therapy where twice daily dosing may have contributed to a further reduction in IOP.

**PACEF Recommendations:**

**Bimatoprost 300mcg/ timolol 5mg per ml eye drops (*Ganfort*), latanoprost 50mcg/ timolol 5mg per ml eye drops (generic) and travoprost 40mcg/ timolol 5mg per ml drops (*DuoTrav*) are all approved for use on the *Lincolnshire Joint Formulary*; designation AMBER without shared care. Latanoprost 50mcg/ timolol 5mg per ml eye drops should always be prescribed generically, not as *Xalacom*. Where a combination PGA/BB preparation is indicated local ophthalmologists prefer bimatoprost 300mcg/ timolol 5mg per ml eye drops (*Ganfort*) and travoprost 40mcg/ timolol 5mg per ml drops (*DuoTrav*).**

(3) Carbonic anhydrase inhibitors (CAIs)

If after adding a BB to a PGA, clinical response remains insufficient a carbonic anhydrase inhibitor should be considered. Also, newly diagnosed cases of early or moderate COAG where only one eye is affected may be better treated first line with either a CAI or a BB (if there are no contraindications). The currently available CAI containing products, including licensed indications, doses and comparative costs are tabulated below:

Carbonic anhydrase inhibitors	Licensed indications	Recommended dose	Cost
Brinzolamide 1% eye drops ( <i>Azopt</i> )	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in COAG or OHT	One drop into the affected eye two or three times a day	5ml £6.92 Patent expired: Dec 2014
Dorzolamide 2% eye drops (generic)	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in OHT, COAG or pseudo-exfoliative glaucoma	One drop into the affected eye two or three times a day	5ml £2.52
Dorzolamide 2% eye drops ( <i>Trusopt</i> )	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in OHT, COAG or pseudo-exfoliative glaucoma	One drop into the affected eye two or three times a day	5ml £6.33
Dorzolamide 2% preservative free single use eye drops ( <i>Trusopt</i> )	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in OHT, COAG or pseudo-exfoliative glaucoma	One drop into the affected eye two or three times a day	60 x 0.2ml £24.18

Carbonic anhydrase inhibitor (CAI) eye preparations containing either brinzolamide or dorzolamide lower IOP by approximately 20%.

**PACEF Recommendations:**

**Dorzolamide 2% eye drops are now available generically at a significantly lower cost than either branded *Trusopt* or brinzolamide 1% eye drops (*Azopt*). However, as dorzolamide 2% eye drops are formulated at a lower pH than brinzolamide, they can be more irritant to the eye causing an unpleasant stinging sensation on application. As a result of this, despite the lower cost of generic dorzolamide, both products are approved for inclusion in the *Lincolnshire Joint Formulary* as possible first line options; designation AMBER without shared care. The single dose preservative free formulation of dorzolamide (*Trusopt*) is also designated as AMBER without shared care, but should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery.”**

#### **(4) Carbonic anhydrase inhibitor/beta blocker combinations**

<b>Carbonic anhydrase inhibitor/beta blocker combination</b>	<b>Licensed indications</b>	<b>Recommended dose</b>	<b>Cost</b>
Brinzolamide 1%/ timolol 0.5% eye drops ( <i>Azarga</i> )	Raised intraocular pressure in COAG or OHT where monotherapy is inadequate	One drop into the affected eye twice daily	5ml £11.05
Dorzolamide 2%/timolol 0.5% eye drops (generic)	Raised intraocular pressure in COAG or OHT where monotherapy is inadequate	One drop into the affected eye twice daily	5ml £2.72
Dorzolamide 2%/ timolol 0.5% eye drops ( <i>Cosopt</i> )	Raised intraocular pressure in COAG or OHT where monotherapy is inadequate	One drop into the affected eye twice daily	5ml £10.05
Dorzolamide 2%/ timolol 0.5% drops preservative-free single use eye drops ( <i>Cosopt</i> )	Raised intraocular pressure in COAG or OHT where monotherapy is inadequate	One drop into the affected eye twice daily	60 x 0.2ml £28.59

#### **PACEF Recommendations:**

**When adding a BB to a CAI, select the combination product containing the same CAI as previously received as monotherapy unless this was not tolerated. The emergence of lower cost generic dorzolamide 2% eye drops and dorzolamide 2%/timolol 0.5% eye drops means that dorzolamide containing preparations should be considered as first line alternatives to brinzolamide 1% eye drops (*Azopt*) and brinzolamide 1%/ timolol 0.5% eye drops (*Azarga*). Lower cost generic dorzolamide 2%/ timolol 0.5% eye drops have already generated fortuitous savings across the county of nearly £70,000pa. A further £28,000pa cost reduction could be achieved by prescribing all dorzolamide 2%/ timolol 0.5% eye drops generically. Both dorzolamide 2%/timolol 0.5% drops (generic) and brinzolamide 1%/timolol 0.5% drops (*Azarga*) are approved for use through the *Lincolnshire Joint Formulary* and designated AMBER without shared care. The single dose preservative free formulation of *Cosopt* is also designated AMBER without shared care,, but should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery.**

#### **(5) Alpha 2 agonists**

In general, alpha 2 agonists are less effective at lowering IOP than PGAs. The range of products available, including licensed indications, doses and prices are tabulated below:

<b>Alpha 2 agonists</b>	<b>Licensed indication</b>	<b>Dose</b>	<b>Price</b>
Apraclonidine 0.5% eye drops ( <i>Iopidine</i> )	Short-term adjunctive treatment of chronic glaucoma to delay laser treatment or glaucoma surgery	One drop into the affected eye three times a day	5ml £10.88
Apraclonidine 1.0% preservative-free single-use eye drops ( <i>Iopidine</i> )	Short-term adjunctive treatment of chronic glaucoma to delay laser treatment or glaucoma surgery	One drop into the affected eye three times a day	24 x 0.25ml £77.85
Brimonidine 0.2% eye drops (generic)	COAG or OHT as monotherapy where BBs are contraindicated or as	One drop into the affected eye twice a day	5ml £2.26

	adjunct to other agents when target IOP is not achieved with a single agent		
Brimonidine 0.2% eye drops ( <i>Alphagan</i> )	COAG or OHT as monotherapy where BBs are contraindicated or as adjunct to other agents when target IOP is not achieved with a single agent	One drop into the affected eye twice a day	5ml £6.85

Local ophthalmologist advice is that alpha 2 agonists should be considered as primary treatment for patients who are non-responders or are allergic to both PGAs and CAIs. They should also be considered as a third medication for patients who have partly responded to treatments with PGAs and CAIs but who decline surgery or in whom surgery is contraindicated.

#### **PACEF Recommendations**

**Generic brimonidine 0.2% eye drops are the preferred alpha 2 agonist eye preparation and are designated AMBER without shared care. The patent expiry of brimonidine 0.2% eye drops (*Alphagan*) has already generated fortuitous savings of £34,000pa across the county as generic prices have fallen. Additional savings could be achieved by ensuring that all remaining prescriptions for *Alphagan* are genericised. Apraclonidine 0.5% solution (*Iopidine*) is also designated AMBER without shared care, but should only be used short-term (a maximum of one month) as an adjunctive treatment of chronic glaucoma to delay laser treatment or glaucoma surgery in patients not adequately controlled with other treatments.**

#### **Alpha 2 agonists/ beta-blocker combination**

Alpha 2 agonists/beta-blocker	Licensed indication	Dose	Price
Brimonidine 0.2%/ timolol 0.5% eye drops ( <i>Combigan</i> )	Reduction in IOP in COAG or OHT insufficiently responsive to topical BBs	One drop into the affected eye twice a day	5ml £10.00 3x5ml £27.00

#### **PACEF Recommendations**

**The alpha 2 agonist/BB combination preparation *Combigan* should only be used for those patients unable to tolerate prostaglandin analogues and carbonic anhydrase inhibitors when treatment with a beta-blocker alone is not adequate. Brimonidine 0.2%/timolol 0.5% eye drops (*Combigan*) is designated AMBER without shared care.**

#### **Carbonic anhydrase inhibitors/ alpha 2 agonist combination**

There is a new CAI/alpha 2 agonist combination product containing brinzolamide 1% and brimonidine 0.2% launched under the brand name *Simbrinza*. Key information is tabulated below:

Carbonic anhydrase inhibitor/Alpha 2 agonists	Licensed indication	Dose	Price
Brinzolamide 1%/brimonidine 0.2% eye drops ( <i>Simbrinza</i> )	Reduction in IOP in COAG or OHT insufficiently responsive to monotherapy.	One drop into the affected eye twice a day	5ml £9.23

### **PACEF Recommendations**

***Simbrinza* should only be used for those patients unable to tolerate alternative combination therapies (i.e prostaglandin analogue/ beta-blocker or carbonic anhydrase inhibitor/ beta blocker).**

### **Systemic treatments**

Acetazolamide 250mg tablets (*Diamox*) and 250mg sustained release capsules (*Diamox SR*) are recommended for short term use as an adjunct to other treatments in people with raised IOP. Oral carbonic anhydrase inhibitors are not recommended for long term use as they can cause agranulocytosis, thrombocytopenia, electrolyte disturbances and metabolic acidosis. Regular monitoring of full blood count and plasma electrolyte count is recommended. Acetazolamide is contraindicated in those patients with a history of allergy to sulphonamides.

### **PACEF Recommendation**

**Both acetazolamide 250mg tablets (*Diamox*) and sustained release capsules (*Diamox SR*) are designated AMBER without shared care for short-term use within licensed indications.**

### **References**

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