NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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What's new this month:

- **Local ophthalmologists have been working with PACEF to develop a formulary of eye preparations for the treatment of open angle glaucoma and raised intra ocular pressure. A review article covers all of the main treatments and their place in therapy (see page 3).**
- **Calcium and vitamin D supplementation is advocated for ambulatory elderly patients in institutionalised care. Guidance is also given on the use of calcium and vitamin D in long-term steroid therapy and in postmenopausal women receiving treatment for the primary or secondary prevention of osteoporotic fragility fractures (see page 9).**
- **A new shared care guideline covering leflunomide in rheumatoid arthritis and active psoriatic arthritis has been approved (see page 12).**

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This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS Lincolnshire website (www.lpct.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: MARCH 2010 UPDATE

Drug	Indication(s)	Traffic Light Status
Prostaglandin analogue eye preparations (PGAs)		
Bimatoprost 0.3mg per ml drops (Lumigan) (3ml bottle)	As monotherapy or as an adjunct to beta-blockers (BBs) in chronic open angle glaucoma (COAG) or ocular hypertension (OHT)	AMBER
Bimatoprost 0.3mg/ timolol 5mg per ml eye drops (Ganfort) (3ml bottle)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	AMBER
Latanoprost 50mcg per ml drops (Xalatan) (2.5ml bottle)	COAG and OHT	AMBER
Latanoprost 0.005%/ timolol 0.5% drops (Xalacom)	OHT and COAG insufficiently responsive to BBs or prostaglandin	AMBER

	analogues	
Tafluprost 15mcg per ml drops (Saflutan) (30 x 0.3ml)	As monotherapy or as an adjunct to BBs in COAG or OHT	AMBER Preservative free preparations should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery
Travoprost 40mcg per ml drops (Travatan) (2.5ml bottle)	OHT and COAG	AMBER
Travoprost 40mcg/ timolol 5mg per ml drops (DuoTrav) (2.5ml bottle)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	AMBER
Carbonic anhydrase inhibitor eye preparations		
Brinzolamide 1% drops (Azopt) (5ml bottle)	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in COAG or OHT	AMBER Carbonic anhydrase inhibitor eye preparation of choice
Brinzolamide 1%/ timolol 0.5% drops (Azarga)	Raised intraocular pressure in COAG or OHT where monotherapy is inadequate	AMBER CAI/BB combination product of choice
Dorzolamide 2% drops (Trusopt) (5ml bottle)	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in OHT, COAG or pseudo-exfolliative glaucoma	AMBER Second line CAI after brinzolamide
Dorzolamide 2% drops (Trusopt) (60 x 0.2ml)	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in OHT, COAG or pseudo-exfolliative glaucoma	AMBER Preservative free preparations should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery
Dorzolamide 2%/ timolol 0.5% drops (Cosopt) (5ml bottle)	Raised intraocular pressure in COAG or OHT where monotherapy is inadequate	AMBER
Dorzolamide 2%/ timolol 0.5% drops single dose containers (Cosopt Preservative Free) (60 x 0.2ml)	Raised intraocular pressure in COAG or OHT where monotherapy is inadequate	AMBER Preservative free preparations should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery
Beta Blocker Eye Preparations		
Timolol 0.25% eye drops (generic) (5ml bottle)	OHT, COAG and secondary glaucoma	AMBER First line BB eye preparation of choice.
Timolol 0.5% eye drops (generic) (5ml bottle)	OHT, COAG and secondary glaucoma	AMBER First line BB eye preparation of choice.
Timolol 0.25% and 0.5% solution in preservative free unit dose vials (Timoptol) (30 x 0.2ml)	OHT, COAG and secondary glaucoma	AMBER Preservative free preparations should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery
Timolol 0.1% gel (Nyogel) (5ml)	OHT and COAG	AMBER Once daily timolol eye preparation of choice
Betaxolol 0.25% suspension (Betoptic) (5ml bottle)	OHT and COAG	AMBER Second line BB after timolol eye drops
Betaxolol 0.5% eye drops (Betoptic Solution) (5ml bottle)	OHT and COAG	AMBER Second line BB after timolol eye drops
Alpha 2 agonist eye preparations		
Brimonidine 0.2% eye drops (Alphagan)	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 Alpha 2 agonist eye preparation of choice
Brimonidine 0.2%/timolol 0.5% eye drops (Combigan)	Reduction in IOP in COAG or OHT insufficiently responsive to topical BBs	AMBER
Apraclonidine 0.5% solution (Iopidine)	Short-term adjunctive treatment of chronic glaucoma to delay laser treatment or glaucoma surgery	AMBER Should only be used for a maximum of one month

Systemic treatments (oral carbonic anhydrase inhibitors)		
Acetazolamide tablets 250mg (Diamox)	Reduction of IOP in COAG, secondary glaucoma and peri-operatively in angle closure glaucoma	AMBER
Acetazolamide capsules MR 250mg (Diamox SR)	Reduction of IOP in COAG, secondary glaucoma and peri-operatively in angle closure glaucoma	AMBER
NICE Appraised Drugs (February 2010)		
Certolizumab pegol injection (Cimzia)	Licensed in combination with methotrexate (MTX) for the treatment of moderate to severe active rheumatoid arthritis (RA) when response to DMARDs including MTX has been inadequate. As monotherapy in RA when MTX is inappropriate or contra-indicated	RED
Trabectedin injection (Yondelis)	Licensed for the treatment of advanced soft tissue sarcoma when treatment with anthracyclines and ifosfamide has failed or is contra-indicated	RED

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care within licensed indications**. Specialist initiation and shared care guidelines are not considered necessary.

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

REVIEW OF GLAUCOMA TREATMENTS

Chronic open angle glaucoma (COAG) is common and potentially blinding; it is usually asymptomatic until advanced. Ocular hypertension is a major risk factor for developing COAG, although COAG can occur with or without raised eye pressure. Approximately 10% of UK blindness registrations are attributed to glaucoma. COAG affects 2% of those over 40 and 10% of white Europeans over 75. Once diagnosed, people with COAG need lifelong monitoring so that any progression of visual damage can be detected. Controlling the condition to prevent or minimise further damage is crucial to maintaining a sighted lifetime.

In response to the publication of NICE Clinical Guideline 85: *Glaucoma – Diagnosis and management of chronic open angle glaucoma and ocular hypertension* (April 2009), PACEF have been working with ULHT ophthalmologists to develop a local formulary of glaucoma treatments and prescribing recommendations. **As a general principle, treatment for COAG and OHT should be initiated by a secondary care based ophthalmologist, although ongoing prescribing may be undertaken by a GP or a non medical prescriber. As a result of this, all approved treatments in the formulary are designated AMBER.**

Prostaglandin analogues (PGAs)

NICE recommend that all people newly diagnosed with early or moderate COAG and at risk of significant visual loss in their lifetime treatment should be offered a prostaglandin analogue (PGA). The currently available products, licensed indications, doses, patent expiry dates and comparative costs are tabulated below:

Prostaglandin analogues	Licensed indications	Recommended dose	Cost
Bimatoprost 0.1mg per ml drops (Lumigan)	**As monotherapy or as an adjunct to BBs in COAG or OHT**	**One drop into the affected eye once daily in the evening**	**3ml £12.43**
Bimatoprost 0.3mg per ml drops (Lumigan)	**As monotherapy or as an adjunct to BBs in COAG or OHT**	**One drop into the affected eye once daily in the evening**	**3ml £10.30 Patent expiry March 2017**
Latanoprost 50mcg per ml drops (Xalatan)	**COAG and OHT**	**One drop into the affected eye once daily in the evening**	**2.5ml £12.48 Patent expiry July 2011**
Tafluprost 15mcg per ml drops (Saflutan)	**As monotherapy or as an adjunct to BBs in COAG or OHT**	**One drop into the affected eye once daily in the evening**	**30 x 0.3ml single use vials £17.41**
Travoprost 40mcg per ml drops (Travatan)	**OHT and COAG**	**One drop into the affected eye once daily in the evening**	**2.5ml £9.98 Patent expiry August 2014**

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

PGAs can cause darkening of the iris in 5 to 20% of patients. Due to this adverse effect, **PGA treatment should normally be reserved for those receiving treatment for both eyes**, unless the patient is happy with the side effects of uniocular use and this is documented in their medical notes. If only one eye is affected, first-line treatment options are either a carbonic anhydrase inhibitor or, if there are no contraindications, a beta-blocker (see below).

All PGAs can 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.

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. **Local ophthalmologists prefer bimatoprost 0.3mg per ml drops (Lumigan) or travoprost 40mcg per ml drops (Travatan) first line.** The cost comparison above reveals that these two products are currently the lowest cost alternatives in primary care. In addition, there is some evidence to suggest that bimatoprost is the most effective product at lowering IOP.

PGAs should not be used in women of child bearing potential unless adequate contraceptive measures are in place. If PGAs need to be used within this context, the prescriber should ensure that patients are informed of the potential risks if they become pregnant and are 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.

PACEF Recommendations

Bimatoprost 0.3mg per ml drops (Lumigan) and travoprost 40mcg per ml drops (Travatan) are designated AMBER. However, PACEF are also mindful of the forthcoming patent expiry of latanoprost 50mcg per ml drops (Xalatan) in July 2011 and are keen to ensure that the potential savings linked to generic latanoprost are fully realised next year. In consequence, latanoprost 50mcg per ml drops (Xalatan) are also designated as AMBER. Local policy will be reviewed with the ophthalmologists within the next year to ensure maximisation of the financial impact of the latanoprost patent

expiry in July 2011. NICE also recommend that preservative-free preparations should be available for patients allergic to preservatives; to accommodate this tafluprost 15mcg per ml drops (Saflutan) are also designated AMBER. Preservative free preparations should be reserved for use only when there is a significant concern that the preservative contained within the eye preparation might be harmful to the eye (e.g. in hypersensitivity or following corneal transplant surgery). Bimatoprost 0.1mg per ml drops (Lumigan) have just been launched; this is a new lower strength formulation of bimatoprost significantly more expensive than standard strength Lumigan. Pending full evaluation, this strength is designated RED-RED.

NICE Recommendations:
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.

Carbonic anhydrase inhibitors (CAIs)

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

Carbonic anhydrase inhibitors	Licensed indications	Recommended dose	Cost
Brinzolamide 1% drops (Azopt)	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 £6.56
Dorzolamide 2% drops (Trusopt)	Monotherapy where BBs are ineffective or contra-indicated or as an adjunct to BBs in OHT, COAG or pseudo-exfolliative glaucoma	One drop into the affected eye two or three times a day	5ml £6.33

Carbonic anhydrase inhibitor (CAI) eye preparations (brinzolamide and dorzolamide) lower IOP by approximately 20%. Dorzolamide 2% drops (Trusopt) present the lowest cost CAI preparation in primary care, although the lower pH of the preparation results in a higher incidence of ocular irritation than brinzolamide 1% drops (Azopt). As a result of this, local ophthalmologists prefer brinzolamide 1% drops (Azopt) first line; where the patient is insufficiently responsive to brinzolamide or where brinzolamide is not tolerated, dorzolamide 2% drops (Trusopt) may present a suitable alternative.

PACEF Recommendation:
Both dorzolamide 2% drops (Trusopt) and brinzolamide 1% drops (Azopt) are designated AMBER. Brinzolamide (Azopt) is the CAI eye preparation of first choice. The single dose preservative free formulation of dorzolamide (Azopt) is designated AMBER, but should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery.

Beta-blockers (BBs)

BBs should be used in accordance with 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 CAI should be considered as first line alternatives. A long acting beta-blocker may also be an option for those patients with uniocular glaucoma. The currently available products, licensed indications, doses and comparative costs are tabulated below:

Beta-Blockers	Licensed indications	Recommended dose	Cost
Betaxolol 0.25% suspension (Betoptic)	**OHT and COAG**	**One drop into the affected eye twice a day**	**5ml £2.66**
Betaxolol 0.5% eye drops (Betoptic Solution)	**OHT and COAG**	**One drop into the affected eye twice a day**	**5ml £1.90**
Betaxolol 0.25% suspension single dose vials preservative-free (Betoptic)	**OHT and COAG**	**One drop into the affected eye twice a day**	**50 x 0.25ml £13.77**
Carteolol 1% eye drops (Teoptic)	OHT, COAG and some secondary glaucomas	One drop into the affected eye twice a day	5ml £4.60
Carteolol 2% eye drops (Teoptic)	OHT, COAG and some secondary glaucomas	One drop into the affected eye twice a day	5ml £5.40
Levobunolol 0.5% drops (generic)	COAG and OHT	One drop into the affected eye once or twice daily	5ml £2.72
Levobunolol 0.5% drops (Betagan)	COAG and OHT	One drop into the affected eye once or twice daily	5ml £1.85
Timolol 0.25% eye drops (generic)	**OHT, COAG and secondary glaucoma**	**One drop into the affected eye twice daily**	**5ml £1.55**
Timolol 0.5% eye drops (generic)	**OHT, COAG and secondary glaucoma**	**One drop into the affected eye twice daily**	**5ml £1.56**
Timolol 0.25% eye drops (Timoptol)	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 (Timoptol)	**OHT, COAG and secondary glaucoma**	**One drop into the affected eye twice daily**	**30 x 0.2ml £8.45**
Timolol 0.5% eye drops (Timoptol)	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 (Timoptol)	**OHT, COAG and secondary glaucoma**	**One drop into the affected eye twice daily**	**30 x 0.2ml £9.65**
Timolol 0.25% eye drops (Timoptol LA)	OHT, COAG and secondary glaucoma	One drop into the affected eye once daily	2.5ml £3.12
Timolol 0.5% eye drops (Timoptol LA)	OHT, COAG and secondary glaucoma	One drop into the affected eye once daily	2.5ml £3.12
Timolol 0.1% gel (Nyogel)	**OHT and COAG**	**One drop in the affected eye(s) daily, preferably in the morning**	**5ml £2.85**

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 the risk of inducing bronchospasm should be appreciated and appropriate precautions taken. Betaxolol is more cardioselective than timolol, but seems to be less effective.

PACEF Recommendations

Timolol maleate eye preparations are approved as the first line BBs of choice. These include generic timolol 0.25% and 0.5% eye drops; both products are designated AMBER. Timolol (Timoptol) solution in preservative free unit dose vials is also designated AMBER in both the 0.25% and 0.5% strengths 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) are approved as a second line alternative to timolol and are designated AMBER. Preservative free betaxolol 0.25% suspension (Betoptic) is also approved as AMBER in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery. Where a once daily timolol eye preparation is indicated, timolol 0.1% gel (Nyogel) is preferred and designated AMBER. Alternative BB formulations including carteolol eye drops 1 and 2% (Teoptic), levobunolol eye drops 0.5% (generic/ Betagan/Betagan Unit Dose) and Timoptol/Timoptol LA formulations are prohibitively expensive and designated RED-RED.

Combination preparations

If adherence and eye drop instillation technique are satisfactory, but IOP has not reduced sufficiently to prevent the risk of progression to sight loss, then a BB should be added to

either a PGA or a CAI. Combination preparations can help to improve adherence, by reducing the number of preparations and doses to be managed by the individual each day. If sufficient clinical response is not obtained after adding a BB to a PGA, a carbonic anhydrase inhibitor should be added.

Prostaglandin analogues/beta-blocker combinations	Licensed indications	Recommended dose	Cost
Bimatoprost 0.3mg/ timolol 5mg per ml eye drops (Ganfort)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	One drop into the affected eye once daily in the morning	3ml £13.95 Patent expiry March 2017
Latanoprost 0.005%/ timolol 0.5% drops (Xalacom)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	One drop into the affected eye once daily	2.5ml £14.32 Patent expiry July 2011
Travoprost 40mcg/ timolol 5mg per ml drops (DuoTrav)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	One drop into the affected eye once daily	2.5ml £12.55 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.

PACEF Recommendations:
All three PGA/BB combination products are designated AMBER with the lower cost preparations in primary care (Ganfort and DuoTrav) preferred by ophthalmologists first line. Local policy will be reviewed with the ophthalmologists within the next year to ensure maximisation of the financial impact of the latanoprost patent expiry in July 2011.

Carbonic anhydrase inhibitors/beta-blockers	Licensed indications	Recommended dose	Cost
Brinzolamide 1%/ timolol 0.5% drops (Azarga)	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% drops (Cosopt)	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 single dose containers (Cosopt Preservative Free)	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 Recommendation:
Both dorzolamide 2%/timolol 0.5% drops (Cosopt) and brinzolamide 1%/timolol 0.5% drops (Azarga) are designated AMBER. As brinzolamide is the CAI of choice, Azarga is preferred. The single dose preservative free formulation of Cosopt is designated AMBER, but should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery.

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.

Alpha 2 agonists

In general, the alpha 2 agonists are less effective at lowering IOP than PGAs.

PACEF Recommendations
Brimonidine 0.2% eye drops (Alphagan) is the preferred alpha 2 agonist eye preparation and is designated AMBER. 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. Apraclonidine 0.5% solution (Iopidine) is designated AMBER, but should only 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	**Licensed indication**	**Dose**	**Price**
Apraclonidine 0.5% solution (Iopidine)	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
Brimonidine 0.2% eye drops (Alphagan)	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
Alpha 2 agonists/ beta-blockers			
Brimonidine 0.2%/timolol 0.5% eye drops (Combigan)	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

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.

Systemic treatments

Acetazolamide 250mg tablets (Diamox) and modified 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 modified release capsules (Diamox SR) are designated AMBER for short-term use within licensed indications.

References
Lincolnshire Joint Formulary, Treatment of open-angle glaucoma
'Treatment of open-angle glaucoma', *Clinical Pharmacist*, 2, March 2010.
Eyawo O et al., Efficacy and safety of PGAs in patients with predominantly primary open-angle glaucoma or OHT: a meta-analysis, Clinical Ophthalmology 2009: 3: 447-56
British National Formulary, 58 (September 2009)

CALCIUM AND VITAMIN D SUPPLEMENTATION

Some controversy remains in Lincolnshire as to whether routine calcium and vitamin D supplementation should be more widely advocated in patients at risk of fracture. Most recently, GPs around Pilgrim Hospital in Boston sought clarification from PACEF following approaches from specialists in secondary care requesting initiation of calcium and vitamin D in all patients in care homes. In response to GP queries, PACEF reconsidered the existing evidence and reviewed new evidence including the new DIPART meta-analysis.

Summary of the evidence

- In 1992 Chapuy determined that giving elderly women living in sheltered accommodation or nursing homes 1200mg calcium and 800 i.u. of vitamin D daily for up to 3 years reduced the relative risk of hip fracture by 43% and non-vertebral fracture by 32%. The 3 year NNT to prevent one hip fracture was between 20 and 40. **From this study we can conclude that 1200mg of calcium and 800 i.u.daily of vitamin D daily can significantly reduce the risk of hip fracture and non-vertebral fracture in elderly women living in care homes and sheltered accommodation.**
- A Cochrane Systematic Review in 2009 concluded that vitamin D (700–800 i.u.) plus calcium reduced the rate of hip fractures in frail older people in institutionalised care, but not in those living in the community. **This suggests that calcium and vitamin D initiatives could usefully be focused around older people living in institutionalised care.**
- Compliance is a significant issue, particularly due to the poor palatability of the products and lack of patient understanding of the potential benefits. A meta-analysis of RCTs found that overall fracture risk reduction was double in trials where the compliance rate was at least 80%. Due to supervised administration, care homes can achieve much higher levels of compliance than unsupervised patients responsible for their own medicines at home.
- A recent meta-analysis of RCTs on the efficacy of oral vitamin D (with or without calcium) in preventing non-vertebral and hip fractures in people over 65 years found that a dose of vitamin D of more than 400 i.u. per day reduced the risk of non-vertebral fractures and hip fractures.
- The recent DIPART meta-analysis concluded that calcium and vitamin D significantly reduced the overall risk of fracture, but only lower doses of vitamin D (400 i.u./day) and calcium reduced the risk of hip fracture. The omission of the Chapuy data from this meta-analysis has caused some to criticise the conclusions. The authors calculated that 213 people would need to be treated with calcium and vitamin D for 3 years to prevent one fracture; for patients over 70 years the NNT was 111.
- In 2009 a meta-analysis reported that doses of vitamin D (700 – 1000 i.u./day) led to a relative risk reduction of falling of 19%. This corresponds to an NNT of 11 to prevent 1 fall over about 21 months. Daily doses of vitamin D less than 700.i.u did not significantly reduce fall risk. **This tends to confirm the standard advice to use calcium and vitamin D formulations that enable doses of vitamin D of 800i.u. to be taken. There is now evidence that vitamin D can help to reduce the risk of non-vertebral and hip fractures and prevent falls.**
- Two Cochrane Systematic Reviews have assessed the evidence supporting interventions to reduce falls in older people in nursing care facilities and hospitals and in the community. They conclude that, in nursing care facilities, falls prevention programmes, the prescription of vitamin D and clinical medication review by a pharmacist may all be effective in reducing the rate of falls. For people in the community, exercise and medication review are effective interventions to reduce the risk and rate of falls; home safety interventions and vitamin D do not appear to reduce rate of falls or risk of falling in the community. There is provisional evidence that vitamin D may reduce falls risk in people with low vitamin D levels.

PACEF Recommendations:

(1) There is now strong evidence to suggest that elderly people living in institutionalised care are likely to benefit from calcium and vitamin D supplementation.

The best evidence is around daily doses of 1200mg of calcium and 800i.u. of vitamin D. Evidence suggests that this can significantly reduce the risk of hip fracture, non-vertebral fracture and falls. It is strongly recommended that all ambulatory patients over the age of 65 currently resident in sheltered accommodation or care homes should be prescribed calcium and vitamin D. Prescribers are encouraged to review all patients in care homes and sheltered accommodation to ensure that calcium and vitamin D supplementation is prescribed for the ambulatory over 65s unless there are compelling reasons not to do so.
(2) Calcium and vitamin D should be prescribed for people on or commencing systemic corticosteroid therapy at any dose for 3 months or longer.
(3) All women on treatment for the primary or secondary prevention of osteoporotic fragility fractures should be prescribed calcium and vitamin D unless dietary intake is considered to be adequate.
(4) Only calcium and vitamin D formulations containing an evidence based dose of each component should be prescribed (i.e. at least 1000mg of calcium and 800i.u. of vitamin D daily). First line preferred products are Adcal-D3 Chewable tablets, Calceos Chewable tablets and Natecal D3 Chewable tablets. Other alternatives are listed below.
(5) Calcichew D3 tablets contain insufficient vitamin D and should not be used for this indication. Existing patients taking Calcichew D3 tablets should be reviewed and stepped up to an approved alternative where indicated.
(6) Other products that should not be used for this indication include: Adcal chewable tablets, Cacit tablets, Calcichew tablets and Calcichew Forte tablets
(7) Cacit D3 effervescent granules are prohibitively expensive and should not be used; several alternative lower cost effervescent formulations are available (see below).
(7) As the dose recommended is supplemental and not pharmacological, routine monitoring is not thought to be necessary except in patients with renal impairment. Calcium and vitamin D should be avoided in patients with hypercalcaemia, metastatic calcification and a history of calcific renal stones.

Product	Dose	Price (28 days)	Flavour
Adcal –D3 Chewable tablets (calcium 600mg/ vit D 400i.u.)	**1 tablet twice daily**	**£3.89**	**Lemon or Tutti Frutti**
Adcal-D3 Dissolve Effervescent tablets (calcium 600mg/vit D 400i.u.)	1 tablet twice daily	£4.99	Lemon
Cacit D3 Effervescent granules (calcium 500mg/ vit D 440i.u.)	2 sachets daily	£7.58	Lemon
Natecal D3 chewable tablets (calcium 600mg/vit D 400i.u.)	**1 tablet twice daily**	**£3.39**	**Aniseed/peppermint**
Calceos Chewable tabs (Calcium 500mg/ vit D 400i.u.)	**1 tablet twice daily**	**£3.38**	**Lemon**
Calcichew D3 Forte Chewable tablets (calcium 500mg, Vit D 400i.u.)	1 tablet twice daily	£4.03	Lemon
Calfovit D3 Sachets (calcium 1200mg/Vit D3 800i.u.)	1 sachet daily	£4.04	Lemon
Sandocal + D 600 effervescent tablets (calcium 600mg/vit D 400iu)	1 tablet twice daily	£4.99	Orange
Sandocal + D 1200 effervescent tablets (calcium 1200mg/vit D 800iu)	1 tablet daily	£4.04	Orange

(Appropriate first line options are highlighted in bold)

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NICE TECHNOLOGY APPRAISAL 185: *TRABECTEDIN FOR THE TREATMENT OF ADVANCE SOFT TISSUE SARCOMA* (FEBRUARY 2010)

Key points are as follows:

Trabectedin is recommended as a treatment option for people with advanced soft tissue sarcoma if:

- treatment with anthracyclines and ifosfamide has failed **or** they are intolerant of or have contraindications for treatment with anthracyclines and ifosfamide
  and
- the acquisition cost of trabectedin for treatment needed after the fifth cycle is met by the manufacturer.

PACEF Recommendation:
Trabectedin injection (Yondelis) is designated RED for this indication.

NICE TECHNOLOGY APPRAISAL 186: *CERTOLIZUMAB PEGOL FOR THE TREATMENT OF RHEUMATOID ARTHRITIS* (FEBRUARY 2010)

Key points are as follows:

Certolizumab pegol is recommended as an option for the treatment of people with rheumatoid arthritis only if:

- certolizumab pegol is used as described for other tumour necrosis factor (TNF) inhibitor treatments in *Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis* (NICE TA 130) **and**
- the manufacturer provides the first 12 weeks of certolizumab pegol (10 pre-loaded 200mg syringes) free of charge to all patients starting treatment.

PACEF Recommendation:
Certolizumab pegol injection (Cimzia) is designated RED for this indication.

NEW TRIALS IN BRIEF

Insulin glargine/ insulin determir and diabetic ketoacidosis

An observational study of 10,682 type 1 diabetics under 20 (mean age 14.2 yrs) undertaken at diabetes centres in Germany and Austria found a higher incidence of diabetic ketoacidosis in those treated with insulin glargine or detemir compared to those treated with NPH insulin.

PACEF Comment:
Prescribers are reminded of guidance from NICE Clinical Guideline 87: *Type 2 diabetes* (May 2009):
Preferably, insulin therapy should be commenced with human NPH insulin injected at bedtime or twice daily according to need [NPH insulin is also known as isophane

insulin; brands of human isophane insulin include Insulatard, Humulin I and Insuman Basal]. A once daily long-acting insulin analogue (i.e. insulin glargine or insulin determir) should only be considered if: (1) the person requires help from a carer or healthcare professional to inject insulin and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily or: (2) the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or: (3)twice-daily NPH insulin injections plus oral glucose-lowering medications would otherwise be needed or: (4) the person cannot use the device to inject NPH insulin.

Reference
Karges B et al. Long acting insulin analogs and the risk of diabetic ketoacidosis in children and adolescents with type 1 diabetes*. Diabetes Care*, published early online.

Do statins increase the risk of developing diabetes?

A meta-analysis of 13 large randomised controlled trials (RCTs) involving statins of at least one years' duration (more than 1000 patients in each RCT; 91,000 total participants) has demonstrated a 9% increased risk of diabetes. Trials involving diabetics were excluded from the meta-analysis. Treatment of 255 patients with statins for 4 years resulted in one extra case of diabetes.

Reference
Sattar N et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *The Lancet* 2010; 375: 735 – 742

SHARED CARE GUIDELINES

PACEF have approved one new shared care guideline this month:

- Leflunomide for the treatment of adult patients with Rheumatoid Arthritis (RA) and for the treatment of active Psoriatic Arthritis (PSA)

Copies are available from Cathy Johnson, Interface Lead Pharmacist at cathy.johnson@lpct.nhs.uk

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (MARCH 2010)

Natalizumab (Tysabri): risk of progressive multifocal leukoencephalopathy increases after 2 years of therapy

- The risk of developing progressive multifocal leukoencephalopathy (PML) with natalizumab increases after 2 years of therapy.
- Progressive multifocal leukoencephalopathy is a rare, progressive and demyelinating disease of the CNS that may be fatal.
- Patients with multiple sclerosis should be informed of the risk before treatment, and again after 2 years. The risk of developing PML beyond 3 years of treatment is currently unknown.
- Continued clinical vigilance for signs and symptoms suggestive of PML is essential (e.g. impaired cognition, visual disturbances, hemiparesis, altered mental state or behavioural changes).
- Natalizumab should be promptly discontinued if PML is suspected.

Fluoxetine: possible small risk of congenital cardiac defects

- Recent epidemiological evidence suggests a possible small increased risk of congenital cardiac defects in association with fluoxetine in early pregnancy, similar to that seen with paroxetine.
- When prescribing fluoxetine to treat depression during pregnancy, prescribers should be aware of this risk.
- The potential increased risk should be balanced against the benefits of treating depression in pregnancy.

- It is possible that this is a class effect, although there is insufficient data to draw this conclusion at present.

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