NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 6; Number 19 **December 2012**

MERRY CHRISTMAS AND A HAPPY NEW YEAR TO ALL OUR READERS

What's new this month?

- **Following in the wake of the *Clopixol Acuphase* incidents, PACEF have been working with LPFT colleagues to secure improved commissioning and supply arrangements for all depot antipsychotic injections for Lincolnshire patients. At present, work is underway to commission the supply and administration of all depot antipsychotic injections through LPFTs community mental health teams. Until this new service is launched in the new year it would be appreciated if all GPs currently prescribing for these patients could continue to do so as an interim arrangement (see page 3).**
- **Following patent expiry, generic latanoprost 50mcg per ml eye drops are now significantly lower in cost than any alternative branded prostaglandin analogue preparation for the treatment of chronic open angle glaucoma (COAG) and ocular hypertension (OHT). Prescribers should ensure that all latanoprost eye drops are prescribed generically. The generic reimbursement price of latanoprost 50mcg/ timolol 5mg per ml eye drops is also beginning to fall; prescribers are urged to ensure that all prescriptions for *Xalacom* are genericised to maximize potential savings (see page 4).**
- **After a review of the latest evidence, oxycodone/naloxone prolonged release tablets (*Targinact*) continue to be designated RED-RED (see page 6).**
- ***Longtec* prolonged release tablets are identical to *Oxycontin* in all key respects and are 15% less expensive. In view of this, oxycodone prolonged release tablets (*Longtec*) are designated GREEN for new patients: product switching from *Oxycontin* to *Longtec* is not encouraged at this time as further new generic and branded generic products are expected in the marketplace in the new year (see page 7).**
- **Both colecalciferol 20,000IU capsules (*Dekristol*) and colecalciferol 20,000IU capsules (*Bio-Vitamin D3*) are designated GREEN for the treatment of severe vitamin D deficiency. *Bio-Vitamin D3* is endorsed as the product of choice (see page 7). An updated summary algorithm on the *Diagnosis and Management of Vitamin D Deficiency in Primary Care* is also provided (see page 8).**
- **Linagliptin/metformin tablets (*Jentadueto*) are not approved for use. Designation: RED-RED (see page 10).**
- **Rifaximin tablets 200mg (*Xifaxanta*) are designated AMBER without shared care for the treatment of hepatic encephalopathy. Rifaximin should be initiated only by a consultant gastroenterologist and will only be used in patients who fail to respond to lactulose. Rifaximin tablets 200mg (*Xifaxanta*) continue to be designated RED-RED for the treatment of non-invasive travellers' diarrhoea (see page 11).**

- **As a result of imminent product discontinuation, all remaining patients on *Mesren MR* 400mg tablets should be switched to *Octasa* 400mg MR tablets at their next prescription. *Mesren MR* 400mg tablets should no longer be initiated in new patients (see page 11).**
- **Both prasugrel 5mg and 10mg tablets (*Efient*) and ticagrelor 90mg tablets (*Brilique*) are designated AMBER without shared care within licensed indications and NICE criteria. Both medicines should only be initiated by a cardiologist (see page 12 to 15).**

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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.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: *OCTOBER 2012 UPDATE*

Drug	Indication(s)	Traffic Light Status
Colecalciferol 20,000IU capsules (*Bio-Vitamin D3*)	Unlicensed product recommended first line for the *treatment* of severe vitamin D deficiency	GREEN Preferred to *Dekristol* as it does not contain arachis (or peanut) oil
Colecalciferol 20,000IU capsules (*Dekristol*)	Unlicensed product recommended first line for the *treatment* of severe vitamin D deficiency	GREEN *Bio-Vitamin D3* is preferred as *Dekristol* contains arachis (or peanut) oil
Ivabradine tablets 5mg and 7.5mg (*Procoralan*)	Licensed for the treatment of stable congestive heart failure (NYHA class II to IV) with systolic dysfunction in patients in sinus rhythm with heart rate ≥75 beats per minute (bpm) in combination with a beta-blocker (BB) or when BB therapy is contraindicated or not tolerated.	AMBER (without shared care)
Linagliptin 2.5mg/ metformin 850mg/1g tablets (*Jentadueto*)	Licensed for the management of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximum tolerated dose of metformin alone or those already	RED-RED

	being treated with a combination of linagliptin and metformin. Licensed in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximum tolerated dose of metformin and a sulfonylurea.	
Mesalazine modified release 400mg tablets (*Octasa*)	For the treatment of mild to moderate acute exacerbations of ulcerative colitis. For the maintenance of remission in UC and Crohn's ileo-colitis.	GREEN
Mesalazine modified release 400mg tablets (*Mesren MR*)	For the treatment of mild to moderate acute exacerbations of ulcerative colitis. For the maintenance of remission in UC and Crohn's ileo-colitis.	RED-RED Product to be withdrawn after 31st December 2012
Oxycodone prolonged release tablets 5mg, 10mg, 20mg, 40mg and 80mg (*Longtec*)	For the treatment of moderate to severe pain in patients with cancer and post-operative pain. For the treatment of severe pain requiring the use of a strong opioid.	GREEN
Oxycodone/naloxone prolonged release tablets 10mg/5mg and 20mg/10mg (*Targinact*)	Licensed for the treatment of severe pain.	RED-RED
Prasugrel tablets 5mg and 10mg (Efient)	Licensed in conjunction with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing primary or delayed percutaneous coronary intervention (PCI)	AMBER without shared care For initiation by cardiologists only
Rifaximin tablets 200mg (*Xifaxanta*)	Licensed for the treatment of non-invasive travellers' diarrhoea	RED-RED
Rifaximin tablets 200mg (*Xifaxanta*)	Unlicensed use for the treatment of hepatic encephalopathy	AMBER without shared care. For initiation by consultant gastroenterologists only.
Ticagrelor 90mg tablets (*Brilique*)	Licensed in combination with aspirin for the prevention of atherothrombotic events in acute coronary syndromes, including patients managed medically with PCI or with coronary artery bypass graft (CABG).	AMBER without shared care. For initiation by consultant gastroenterologists only.

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.**

PRESCRIBING DEPOT ANTIPSYCHOTIC MEDICATION

Following in the wake of the *Clopixol Acuphase* incidents reported in *PACE Bulletin* Volume 6 Number 12 (August 2012), PACEF have been working with LPFT colleagues to secure improved commissioning and supply arrangements for all depot antipsychotic injections for Lincolnshire patients. At present, work is underway to commission the supply and administration of all depot antipsychotic injections through LPFTs community mental health teams. Until this new service is launched in

the new year it would be appreciated if GPs currently prescribing for these patients could continue to do so as an interim arrangement.

UPDATED GUIDANCE ON THE USE OF PROSTAGLANDIN ANALOGUES IN THE TREATMENT OF CHRONIC OPEN ANGLE GLAUCOMA AND OCULAR HYPERTENSION

Prostaglandin analogue eye preparations

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). NICE recommend that all people newly diagnosed with early or moderate COAG and at risk of significant visual loss in their lifetime should be offered a prostaglandin analogue (PGA**).** 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. An updated cost comparison of the various PGA eye drops reveals that generic latanoprost 50mcg per ml eye drops are now significantly lower in cost than any alternative branded PGA preparation (see below):

Prostaglandin analogues	**Licensed indications**	**Recommended dose**	**Cost**
Latanoprost 50mcg per ml drops (generic)	**COAG and OHT**	**One drop into the affected eye once daily in the evening**	**2.5ml £3.89**
Latanoprost 50mcg per ml drops (*Xalatan*)	COAG and OHT	One drop into the affected eye once daily in the evening	2.5ml £12.48
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
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

Ref: *Drug Tariff* (November 2012)

Following a detailed review of this therapy area with ULH consultant ophthalmologists, the following changes to local guidance have been agreed:

- Generic latanoprost eye drops 50mcg per ml will be used first-line for the treatment of glaucoma or raised intraocular pressure (IOP) in patients with early, mild disease.
- Bimatoprost or travoprost will be considered as 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. Latanoprost is not as well tolerated as alternative PGA products due to the high level of benzalkonium (BAK) preservative present in both the generic and branded formulations. Travoprost has a different non-BAK preservative which can be better tolerated by the ocular surface and bimatoprost 0.003% has approximately a quarter of the preservative of *Xalatan.*
- Published clinical data suggests that all three prostaglandin products produce similar reductions in IOP, although, in practice, local ophthalmologists have tended to prefer bimatoprost or travoprost in patients requiring greater reduction in IOP or more rapid disease control. As a result of this, in more established

disease when control needs to be achieved quickly to preserve remaining vision bimatoprost or travoprost may be used preferentially first-line.

- All patients currently prescribed *Xalatan* eye drops by brand should be changed to generic latanoprost eye drops. A joint statement from the Royal College of Ophthalmologists and the ophthalmology group of the Royal Pharmaceutical Society has concluded that the constituents of the various generic latanoprost products are similar to those of *Xalatan* and that bioavailability of the various generics should be similar. Nonetheless, patients should be informed of the change as the appearance of the eye drop bottle may differ from *Xalatan* and there may be differences in storage requirements. It is possible that patients who previously tolerated *Xalatan* or a particular generic product may develop an intolerance or allergic reaction to the new product. If this occurs the patient should be switched back to branded Xalatan.
- Patients currently prescribed other PGAs, such as travoprost or bimatoprost, should not be switched to generic latanoprost unless they are either not achieving an adequate clinical response from their current medication or are unable to tolerate their current product; generic latanoprost may be considered an option if the patient has not previously received latanoprost.

Combination PGA/beta-blocker (BB) eye 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 a PGA. Combination PGA/BB 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.

An updated cost comparison of the PGA/BB combination eye preparations available reveals that generic latanoprost 50mcg/timolol 5mg per ml (*Xalacom*) eye drops are now significantly lower in cost than any alternative branded PGA/BB preparation (see below):

Prostaglandin analogues/beta-blocker combinations	**Licensed indications**	**Recommended dose**	**Cost**
Latanoprost 50mcg/ timolol 5mg per ml drops (generic)	**OHT and COAG insufficiently responsive to BBs or prostaglandin analogues**	**One drop into the affected eye once daily**	**2.5ml £10.88**
Latanoprost 50mcg/ timolol 5mg per ml (*Xalacom*)	OHT and COAG insufficiently responsive to BBs or prostaglandin analogues	One drop into the affected eye once daily	2.5ml £14.32
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
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

Similarly, the following changes to local guidance have been agreed:

- Where a particular PGA eye preparation is used and the addition of a beta blocker is required, the corresponding PGA/BB combination product should be used. Where latanoprost 50mcg per ml eye drops require the addition of a beta blocker, generic latanoprost 50mcg/ timolol 5mg per ml drops should be used first-line.

- All patients currently prescribed *Xalacom* eye drops by brand should be changed to generic latanoprost 50mcg/ timolol 5mg per ml drops. Patients should be informed of the change as the appearance of the eye drop bottle may differ from *Xalacom* and there may be differences in storage requirements. It is possible that patients who previously tolerated *Xalacom* or a particular generic product may develop an intolerance or allergic reaction to the new product. If this occurs the patient should be switched back to branded *Xalacom.*

PACEF Recommendation:
Following patent expiry, generic latanoprost 50mcg per ml eye drops are now significantly lower in cost than any alternative branded prostaglandin analogue preparation for the treatment of chronic open angle glaucoma (COAG) and ocular hypertension (OHT). Prescribers should ensure that all latanoprost eye drops are prescribed generically. The generic reimbursement price of latanoprost 50mcg/ timolol 5mg per ml eye drops is also beginning to fall; prescribers are urged to ensure that all prescriptions for *Xalacom* are genericised to maximize potential savings.

RAPID REVIEW: *OXYCODONE/ NALOXONE PROLONGED RELEASE TABLETS (TARGINACT)*

Targinact is a prolonged release (PR) tablet formulation of oxycodone in combination with naloxone; it is licensed for the treatment of severe pain. The theory behind this combination is that the opioid antagonist, naloxone, will counteract the opioid induced constipation associated with oxycodone. There is some evidence from published trials that *Targinact* marginally reduces laxative use in some patients without any impairment of analgesic effect or symptoms of opioid withdrawal. However no comparative studies have yet been published comparing *Targinact* with separate opioid/laxative combination therapy. Most published studies are short-term; there has been one 52 week observational non-blinded follow-up study, a 4 week observational study in 7836 patients with severe pain including cancer pain and a 4 week randomised controlled trial in 185 patients with moderate to severe cancer pain.
A *Drug and Therapeutics Bulletin* review published in 2010 concluded that, given the evidence available, 'we can see no reason why *Targinact* should be prescribed. Published evidence cited to support the promotional claims that *Targinact* provides "better pain relief", "superior gastrointestinal tolerability" and "improved quality of life" "compared to previous treatment in a clinical practice study (n=7836)" is not convincing'. In addition, *Targinact* is expensive in comparison to other opioids and standard laxatives, a situation that is further complicated by the falling price of oxycodone as we approach patent expiry (see *Longtec* assessment).

Targinact has now been assessed three times by PACEF and ULH Drug and Therapeutics Committee in 2009, 2010 and September 2012. Both PACEF and ULH DTC agree that there is still no new evidence necessitating a change to our existing position.

PACEF Recommendation:
In published trials, oxycodone/naloxone (*Targinact*) has been shown to marginally reduce laxative use in some patients without any impairment of analgesic effect or symptoms of opioid withdrawal. However, no comparative studies have yet been published comparing *Targinact* with separate opioid/laxative combination therapy. In addition, the short-term nature of existing studies provides no assurance of long-term safety. The cost in comparison to other opioids and standard laxatives is excessive, particularly

as many of the patients prescribed *Targinac*t still require concurrent laxative treatment. Further concerns over the cost of *Targinact* are emerging related to the falling price of oxycodone as we approach patent expiry. Fixed dose combination analgesics can also create problems during incremental dose adjustment and titration as it is impossible to adjust the dose of one component without adjusting the dose of both. After re-consideration of all these factors oxycodone/naloxone PR tablets (*Targinact*) continue to be designated: RED-RED.

RAPID DRUG ASSESSMENT: *OXYCODONE PROLONGED RELEASE TABLETS (LONGTEC)*

Longtec is the brand name for a generic prolonged release range of oxycodone tablets recently launched by Qdem Pharmaceuticals Ltd. The product is manufactured under license from the manufacturer of the originator brand, *Oxycontin* (Napp). Qdem have launched *Longtec* in five strengths, 5mg, 10mg, 20mg, 40mg and 80mg, all of which appear identical in shape and colour to *Oxycontin*, have identical blister packaging and are even manufactured in the same factory. *Oxycontin* is available in a wider range of strengths, but is 15% more expensive than *Longtec* (see cost comparison below):

Drug	Dose	Cost
Oxycodone prolonged release tablets 5mg (*Longtec*)	**5mg every 12 hours**	**£21.26 (2x28's)**
Oxycodone prolonged release tablets 10mg (*Longtec*)	**10mg every 12 hours**	**£21.24**
Oxycodone prolonged release tablets 20mg (*Longtec*)	**20mg every 12 hours**	**£42.48**
Oxycodone prolonged release tablets 40mg (*Longtec*)	**40mg every 12 hours**	**£84.98**
Oxycodone prolonged release tablets 80mg (*Longtec*)	**80mg every 12 hours**	**£169.97**
Oxycodone prolonged release tablets 5mg (*Oxycontin*)	5mg every 12 hours	£25.00
Oxycodone prolonged release tablets 10mg (*Oxycontin*)	10mg every 12 hours	£24.99
Oxycodone prolonged release tablets 15mg (*Oxycontin*)	15mg every 12 hours	£37.41
Oxycodone prolonged release tablets 20mg (*Oxycontin*)	20mg every 12 hours	£49.98
Oxycodone prolonged release tablets 30mg (*Oxycontin*)	30mg every 12 hours	£74.81
Oxycodone prolonged release tablets 40mg (*Oxycontin*)	40mg every 12 hours	£99.98
Oxycodone prolonged release tablets 60mg (*Oxycontin*)	60mg every 12 hours	£149.66
Oxycodone prolonged release tablets 80mg (*Oxycontin*)	80mg every 12 hours	£199.97
Oxycodone prolonged release tablets 120mg (*Oxycontin*)	120mg every 12 hours	£299.31

Undeniably, *Longtec* is available in fewer strengths than *Oxycontin*, although the most widely prescribed strengths of *Oxycontin* are available in the *Longtec* range. Other branded generic prolonged release oxycodone preparations are beginning to appear in anticipation of patent expiry (e.g. Oxylan)

PACEF Recommendation:
***Longtec* prolonged release tablets are identical to *Oxycontin* in all key respects and are 15% less expensive. In view of this, oxycodone prolonged release tablets (*Longtec*) are designated GREEN for new patients: product switching from *Oxycontin* to *Longtec* is not encouraged at this time as further new generic and branded generic products are expected in the marketplace in the new year. All *Longtec* prescribing should be by brand to ensure that the specific product is dispensed and that savings are realised. It is acknowledged that *Oxycontin* is available in a wider range of strengths and will continue to be necessary for some patients.**

RAPID DRUG ASSESSMENT: *COLECALCIFEROL 20,000IU CAPSULES (BIO-VITAMIN D3)*

Colecalciferol 20,000IU capsules (*Bio-Vitamin D3*) is a high dose vitamin D supplement comparable in strength to *Dekristol*. It is not a licensed medicine and is classed as a food supplement. Existing PACEF advice on the treatment of severe vitamin D deficiency reads as follows:

- Colecalciferol 20,000IU capsules (*Dekristol*) (60,000IU weekly (3 capsules) weekly for 12 weeks) are recommended first line for the treatment of severe vitamin D deficiency (<25 nmol/l 25 hydroxyvitamin D) (see *PACE Bulletin*, Vol 6, No 19 (October 2012))

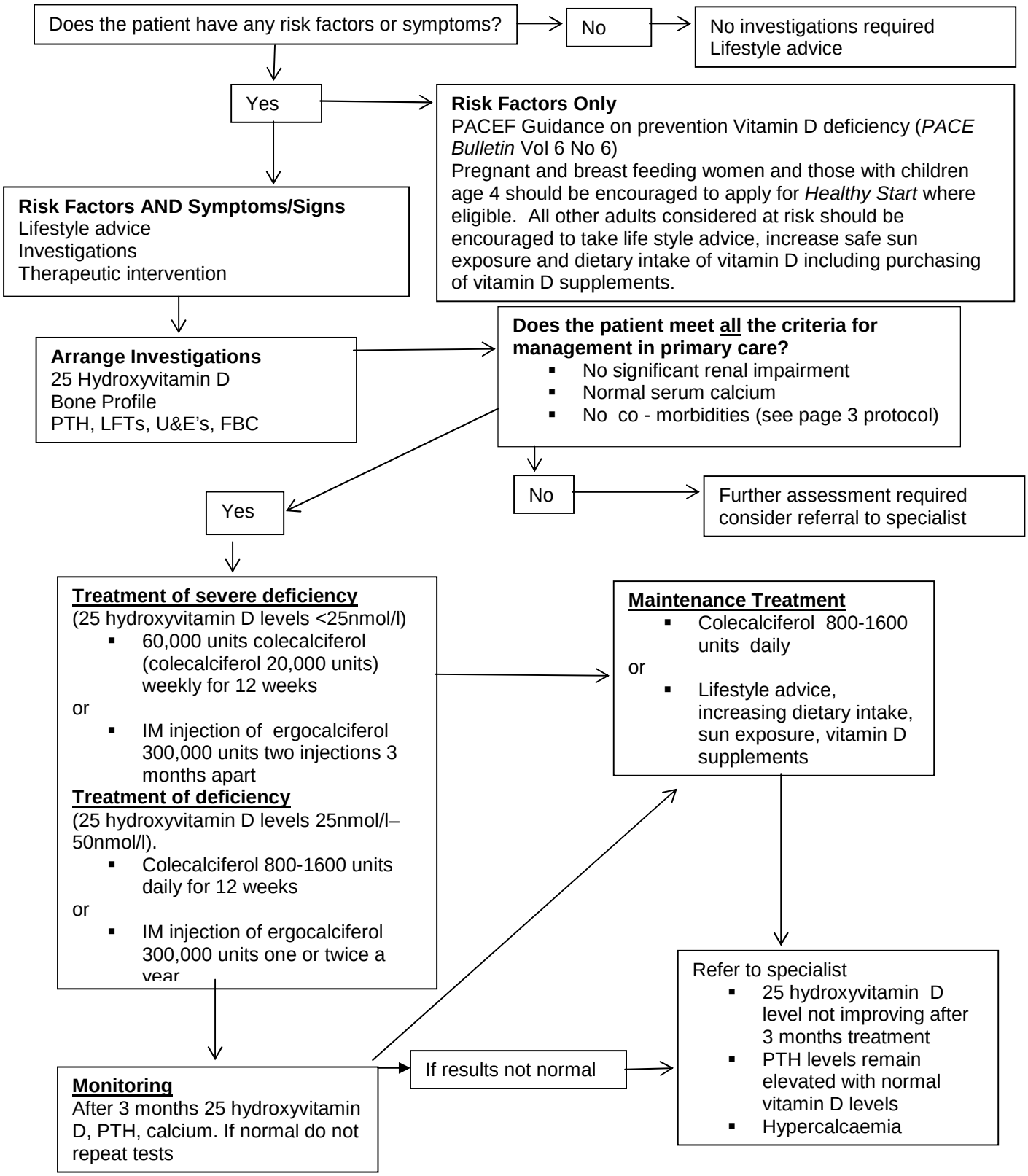
Dekristol is a licensed medicine in Germany. According to the MHRA hierarchy of risks associated with the use of unlicensed medicines, an imported product licensed in its country of origin is preferable to an unlicensed special or, as in this case, an unlicensed food supplement. Nonetheless, the advocacy of *Dekristol* first line within this context has presented some problems. Some practices and pharmacies have struggled to source the product, although it is now in stock at Maltby's. Secondly, a recent MHRA safety warning to all prescribers advised that *Dekristol* contains arachis (or peanut) oil and urged avoidance in those with a nut allergy. *Bio-Vitamin D3* does not contain arachis oil and presents a better option for patients with an allergy to nuts. A cost comparison reveals that *Bio-Vitamin D3* is comparable in price to *Dekristol.*

PACEF Recommendation:
Both colecalciferol 20,000IU capsules (*Dekristol*) and colecalciferol 20,000IU capsules (*Bio-Vitamin D3*) are designated GREEN for the treatment of severe vitamin D deficiency. *Bio-Vitamin D3* is endorsed as the product of choice as it is comparable in price to *Dekristol*, but does not have the patient safety issues associated with the inclusion of arachis oil in the formulation. PACEF are acutely aware of the number of product launches pending in this rapidly developing disease area and will endeavour to issue assessments on all new vitamin D3 products as they come to market. An updated version of the summary algorithm on the *Diagnosis and Management of Vitamin D Deficiency in Primary Care* follows.

SUMMARY ALGORITHM: *DIAGNOSIS AND MANAGEMENT OF VITAMIN D DEFICIENCY IN PRIMARY CARE*

Population screening by measuring vitamin D levels is unnecessary, even in high risk populations. For information on different colecalciferol preparations please refer to the list available through the PACEF section of the NHS Lincolnshire website

(www.lincolnshire.nhs) or contact a member of the Prescribing and Medicines Optimisation Team.



RAPID DRUG ASSESSMENT: *LINAGLIPTIN 2.5MG/METFORMIN 850MG/1G FILM COATED TABLETS (JENTADUETO)*

Jentadueto is a combination product containing linagliptin 2.5mg in combination with either 850mg or 1g of metformin. It is licensed:

- for the management of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximum tolerated dose of metformin alone or those already being treated with a combination of linagliptin and metformin.
- in combination with a sulfonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximum tolerated dose of metformin and a sulfonylurea.

Evidence from one multicentre randomised trial demonstrated that linagliptin in combination with metformin provides a greater reduction in HbA1c levels after 6 months treatment than was achieved with the individual components prescribed separately. It is also claimed that combination products like *Jentadueto* provide an opportunity to reduce the tablet burden and potentially improve patient compliance in those who require linagliptin in combination with metformin to improve their hypoglycaemic control.

A cost comparison reveals the following:

Drug	Daily dose	Cost 28 days
Combination gliptin with metformin		
Linagliptin 2.5mg/ metformin 850mg tablets (*Jentadueto*)	1 twice daily	£33.26
Linagliptin 2.5mg/ metformin 1000mg tablets (*Jentadueto*)	1 twice daily	£33.26
Sitagliptin 50mg/ metformin 1000mg tablets (*Janumet*)	1 twice daily	£34.56
Vildagliptin 50mg/ metformin 850mg tablets (*Eucreas*)	1 twice daily	£33.98
Vildagliptin 50mg/ metformin1000mg tablets (*Eucreas*)	1 twice daily	£33.98
Individual drugs		
Linagliptin 5mg tablets (*Trajenta*)	5mg once daily	£33.26
Saxagliptin 2.5mg tablets (*Onglyza*)	2.5mg once daily	£31.60
Saxagliptin 5mg tablets (*Onglyza*)	5mg once daily	£31.60
Sitagliptin 100mg tablets (*Januvia*)	100mg once daily	£33.26
Vildagliptin 50mg tablets (*Galvus*)	50mg twice daily (with metformin or glitazone)	£31.76
Vildagliptin 50mg tablets (*Galvus*)	50mg daily (with sulfonylurea)	£15.85
Metformin 850mg tablets	1 twice daily	£1.06
Metformin 500mg tablets	2 tablets twice daily	£2.76

All three of the dipeptidyl peptidase 4 (DPP4) inhibitor combination products are comparably priced, with *Jentadueto* marginally lower in cost than the other two, *Janumet* and *Eucreas*. *Jentadueto* is also priced comparably with linagliptin alone and is the only one of the three combination products that is lower in cost than the components prescribed separately.

PACEF undertook a detailed review of the DPP4 inhibitors which was published in the *PACE Bulletin* in January 2012 (Vol 6, No 3). One of the outcomes of that review was that linagliptin (*Trajenta*) was evaluated as the most appropriate DPP-4 inhibitor for use in patients with renal or hepatic impairment as linagliptin undergoes minimal

elimination via the renal route. However, due to its higher comparative cost, particularly in comparison to saxagliptin, it was not approved for first line use (where a DPP4 inhibitor is indicated).

PACEF Recommendation:
At present, linagliptin (*Trajenta*) is only approved for use in patients with renal or hepatic impairment. As metformin should be used with caution in renal and hepatic impairment, linagliptin/metformin tablets (*Jentadueto*) are not approved for use. Designation: RED-RED. PACEF continue to keep DPP-4 inhibitors under review as new evidence continues to emerge.

NEW INDICATION ASSESSMENT: *RIFAXIMIN 200MG TABLETS* (*XIFAXANTA*)

Rifaximin (*Xifaxanta*) is a semi-synthetic derivative of the antibiotic rifamycin, which is licensed for the treatment of non-invasive traveller's diarrhoea. PACEF reviewed the product for this indication in April 2012 and designated it RED-RED (see *PACE Bulletin* Vol 6 No 7 (May 2012)).

In addition, rifaximin decreases intestinal production and absorption of ammonia which is thought to be responsible for the neurocognitive symptoms of hepatic encephalopathy and has been shown to be effective in delaying the recurrence of acute episodes. It has been studied in clinical trials as monotherapy or in combination with lactulose for the treatment of adults with liver disease who have had prior acute episodes of hepatic encephalopathy (grade II-IV). A recent study showed that over a 6-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than placebo. Rifaximin treatment also significantly reduced the risk of hospitalization due to hepatic encephalopathy. The incidence of adverse events was similar in the rifaximin group and the placebo group. The cost of the treatment is £266.40 per month. Rifaximin (*Xifaxanta*) does not currently have a UK marketing authorisation for the maintenance treatment of hepatic encephalopathy.

PACEF Recommendation:
Rifaximin tablets 200mg (*Xifaxanta*) are designated AMBER without shared care for the treatment of hepatic encephalopathy. Rifaximin should be initiated only by a consultant gastroenterologist and will only be used in patients who fail to respond to lactulose. Rifaximin tablets 200mg (*Xifaxanta*) continue to be designated RED-RED for the treatment of non-invasive travellers' diarrhoea.

WITHDRAWAL OF MESALAZINE MODIFIED RELEASE 400MG TABLETS (*MESREN MR*)

IVAX have announced the discontinuation of mesalazine MR 400mg tablets (*Mesren MR*) after the 31st December 2012. In November Tillotts launched a 400mg strength of *Octasa* MR which is exactly the same formulation as *Mesren MR* and is even made in the same factory. The two products are exactly the same price.
Tilllots are producing a patient information leaflet and template letters to provide reassurance to patients that despite the change in brand name and packaging, the appearance of the mesalazine tablet and efficacy of the product remains unaltered. There is a website (www.ucandme.co.uk) which aims to provide further information for both patients and health care professionals. Very few patients in Lincolnshire are currently prescribed *Mesren MR*, so it is envisaged that the impact of this product withdrawal in county will be very slight.

PACEF Recommendation:
As a result of imminent product discontinuation, all remaining patients on *Mesren MR* 400mg tablets should be switched to *Octasa* 400mg MR tablets at their next prescription. *Mesren MR* 400mg tablets should no longer be initiated in new patients. Due to differences in bioavailability, site of action and cost, it is recommended that all prescriptions for mesalazine oral products should be prescribed by brand to avoid any unnecessary confusion. PACEF are in the process of reviewing current advice on the prescribing of all oral mesalazine products and updated guidance will appear in the *PACE Bulletin* early in the new year.

NEW TRIAL ASSESSMENT

IVABRADINE AND HEART FAILURE

Ref: Borer JS et al. Effect of ivabradine on recurrent hospitalisation for worsening heart failure in patients with chronic systolic heart failure: the SHIFT study. *European Heart Journal* doi: 10.1093/eurheart/ehs259

This is a post hoc analysis of the Systolic Heart Failure Treatment with If Inhibitor Ivabradine Trial (SHIFT). SHIFT has previously been reviewed by PACEF as part of our New Indication Assessment of ivabradine (*Procoralan*) in heart failure (see *PACE Bulletin* Vol 6 No 12 (August 2012)). This post hoc analysis looked at hospitalisations for worsening heart failure in patients admitted multiple times during the 2 year trial period. It revealed that ivabradine patients were at a lower risk of suffering a second or third hospitalisation for worsening heart failure compared to placebo.

PACEF Recommendation:
This post hoc analysis of SHIFT consolidates the current PACEF position on ivabradine in heart failure. Ivabradine tablets 5mg and 7.5mg (Procoralan) may be an appropriate adjunct to optimal BB /ACEI therapy in patients unable to achieve sufficient heart rate reduction on standard therapy or for those in whom BBs are not tolerated or contraindicated and who still have a high pulse rate. As a result of this, ivabradine is approved for the treatment of CHF within the terms of its marketing authorisation (i.e. for stable CHF (NYHA class II to IV) with systolic dysfunction in patients in sinus rhythm with heart rate ≥75 beats per minute (bpm) in combination with a beta-blocker (BB) or when BB therapy is contraindicated or not tolerated). Treatment should only be initiated by a physician who is experienced in the management of heart failure. Designation: AMBER (without shared care).

NICE UPDATE

REVIEW OF NICE TECHNOLOGY APPRAISAL 182: *PRASUGREL FOR THE TREATMENT OF ACUTE CORONARY SYNDROMES WITH PERCUTANEOUS CORONARY INTERVENTION* (OCTOBER 2009)

Key Recommendations

Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention only when:

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction (STEMI) is necessary or

- stent thrombosis has occurred during clopidogrel treatment or the patient has diabetes mellitus.

This guidance is based on a NICE evaluation of the TRITON-TIMI 38 study. TRITON-TIMI 38 shows some advantages with prasugrel in terms of effectiveness, including statistically significant reductions in a composite endpoint, non-fatal MI and stent thrombosis compared to clopidogrel. In terms of safety, an increased rate of major bleeds (including fatal bleeds) occurred with prasugrel compared with clopidogrel. Overall, all-cause mortality, CV death and non-fatal stroke did not differ significantly between groups. NICE conclude that prasugrel and clopidogrel are broadly equivalent in terms of clinical effectiveness at 15 months for patients with ACS having PCI.

In terms of cost-effectiveness, NICE conclude that prasugrel is only cost-effective in the sub-groups identified above. Since the TA was published the cost differential between the clopidogrel and prasugrel has widened markedly:

Drug	Daily dose	28 day cost
Prasugrel 5mg tablets (*Efient*)	5mg daily	£47.56
Prasugrel 10mg tablets (*Efient*)	10mg daily	£47.56
Clopidogrel 75mg tablets (generic)	75mg daily	£1.95

PACEF Recommendation:
PACEF guidance on the use of antiplatelet agents is in preparation and will be published early in the new year. Nonetheless, PACEF recognise that the newer agents prasugrel and ticagrelor are already in wider use within NICE criteria initiated by secondary and tertiary care cardiologists outside of the county. For example, within Hull and East Riding, prasugrel is initiated by cardiologists for the prevention of atherothrombotic events in patients with Acute Coronary Syndrome (ACS) undergoing percutaneous coronary intervention (PCI), in the following circumstances: (1) As a loading dose for in-patients with acute STEMI and NSTEMI undergoing PCI who are unsuitable for treatment with ticagrelor and (2) As ongoing treatment (in combination with aspirin 75mg) in patients who are unsuitable for treatment with ticagrelor AND with an allergy to clopidogrel, or where there is a history of stent thrombosis during treatment with clopidogrel. In acknowledgement of this and in anticipation of forthcoming Lincolnshire guidance, prasugrel (*Efient*) is designated as AMBER without shared care within licensed indications and NICE criteria. Prasugrel (*Efient*) should only be initiated by a cardiologist.

NICE TECHNOLOGY APPRAISAL 236: *TICAGRELOR FOR THE TREATMENT OF ACUTE CORONARY SYNDROMES* (OCTOBER 2011)

Key Recommendations

Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes (ACS) that is, people:

- with **ST-segment-elevation myocardial infarction (STEMI)** – defined as ST elevation or new left bundle branch block on electrocardiogram – **that cardiologists intend to treat with primary percutaneous coronary intervention (PCI)** or:
- with **non-ST-segment-elevation myocardial infarction (NSTEMI)** or:

- admitted to hospital with **unstable angina** – defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus one of the characteristics defined below. **Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.**

For the purposes of this guidance, characteristics to be used in defining treatment with ticagrelor for unstable angina are:

- age 60 years or older;
- previous myocardial infarction or previous coronary artery bypass grafting (CABG);
- coronary artery disease with stenosis of 50% or more in at least two vessels;
- previous ischaemic stroke;
- previous transient ischaemic attack,
- carotid stenosis of at least 50%, or cerebral revascularisation;
- diabetes mellitus;
- peripheral arterial disease;
- or chronic renal dysfunction, defined as a creatinine clearance of less than 60 ml per minute per 1.73 m^2 of body-surface area.

NICE reviewed the Platelet Inhibition and Patient Outcomes Study (PLATO) as the only trial relevant to this decision problem. PLATO evaluated the efficacy and safety of ticagrelor plus aspirin compared to clopidogrel plus aspirin over 12 months in people with ACS whose symptoms began up to 24 hours before hospital admission. 18,624 adult patients with ACS with or without ST segment elevation were randomised to either:

- ticagrelor 180mg loading dose followed by 90mg twice daily or
- clopidogrel 300 to 600mg loading dose then 75mg daily thereafter.

All patients were also taking aspirin 75 to 100mg daily.

The primary end point was time to first event (composite of MI, stroke or death from vascular causes). The secondary end points were: MI, stroke, death from vascular causes, death from any cause, composite of MI, stroke and death from any cause, composite of MI, stroke, severe recurrent cardiac ischaemia, TIA, other arterial thrombotic events and death from vascular causes.

Randomisation to ticagrelor plus aspirin reduced the absolute risk of experiencing the primary end point from 11.7% to 9.8% (Absolute Risk Reduction 1.9%) compared with clopidogrel plus aspirin (the Number Needed to Treat is 53 over 12 months (i.e 53 patients with ACS would have to be treated with ticagrelor rather than clopidogrel for 12 months in order to prevent one additional event)).

No significant difference in major bleeding (the primary safety variable) was found between groups (ticagrelor 11.6%; clopidogrel 11.2%). However, ticagrelor was associated with a significantly increased risk of major bleeding not related to CABG (4.5% vs 3.8%; Number Needed to Harm 143); patients randomised to ticagrelor also experienced more major and minor bleeding overall (including intracranial bleeding). Patients treated with ticagrelor also experienced more dyspnoea, ventricular pauses (of 3 seconds or longer) and increases in serum creatinine and uric acid than clopidogrel; a patient randomised to ticagrelor was nine times as likely to discontinue treatment due to dyspnoea than a patient randomised to clopidogrel.

In terms of cost-effectiveness, NICE conclude that ticagrelor is cost-effective in the sub-groups identified above. A cost comparison with generic clopidogrel reveals the following:

Drug	Daily dose	28 day cost
Ticagrelor 90mg tablets (*Brilique*)	90mg twice daily	£54.60
Clopidogrel 75mg tablets (generic)	75mg daily	£1.95

PACEF Recommendation:

PACEF guidance on the use of antiplatelet agents is in preparation and will be published early in the new year. Nonetheless, PACEF recognise that the newer agents prasugrel and ticagrelor are already in wider use within NICE criteria initiated by secondary and tertiary care cardiologists outside of the county. For example, within Hull and East Riding, ticagrelor is initiated by cardiologists for prevention of atherothrombotic events in patients with ACS undergoing PCI in the following circumstances: (1) a loading dose of 180mg for in-patients with acute STEMI undergoing primary PCI and moderate to high risk NSTEMI undergoing PCI. Patients will also receive an aspirin loading dose of 300mg; (2) a maintenance dose of 90mg twice daily (in combination with aspirin 75mg). Ticagrelor will not normally be used for troponin negative ACS patients. In acknowledgement of this and in anticipation of forthcoming Lincolnshire guidance, ticagrelor (Brilique) is designated as AMBER without shared care within licensed indications and NICE criteria. Ticagrelor (Brilique) should only be initiated by a cardiologist.

Acknowledgements

Many thanks to Cathy Johnson, Interface Lead Pharmacist, NHS Lincolnshire, the consultant ophthalmologists at United Lincolnshire Hospitals Trust (ULH), Robyn Thompson, Senior Pharmacist , ULH, and Gill Kaylor, Prescribing Adviser, NHSL, for their help in the compilation of this *Bulletin*.

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December 2012