Greater East Midlands
Commissioning Support Unit

Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 10 **June 2013**

What's new this month?

- **The *Viagra* patent is due to expire in June 2013 followed by the launch of lower cost generic sildenafil tablets 25mg, 50mg and 100mg. Prescribers should ensure that generic sildenafil tablets are used as the first line PDE5 inhibitor of choice for the treatment of erectile dysfunction. All remaining branded prescribing of *Viagra* should be switched to generic sildenafil. Existing patients taking alternative branded PDE5 inhibitors (tadalafil (*Cialis*) and vardenafil (*Levitra*)) should be reviewed at their next appointment with a view to ensuring that sildenafil naïve patients are switched to sildenafil where appropriate (see page 4).**
- **Pioglitazone 15mg/metformin 850mg tablets (*Competact*) are significantly over-priced in relation to the generically available separate components, metformin 850mg tablets and pioglitazone tablets. All existing patients on *Competact* should be reviewed with a view to prescribing constituent components separately wherever possible. There should be no new initiations of *Competact* which is now designated RED-RED for new patients (see page 5).**
- **Tapentadol prolonged release tablets (*Palexia SR*) have been re-assessed, but continue to be designated RED-RED (see page 5).**
- **Rifaximin tablets 550mg *(Targaxan)* for the reduction in recurrence of overt hepatic encephalopathy have been assessed and are now advocated in preference to unlicensed rifamixin (*Xifaxanta*) for this indication. Designation: AMBER (see page 7).**
- **NICE have not approved the use in the NHS of tadalafil (*Cialis*) for the treatment of symptoms associated with benign prostatic hyperplasia. As a result of this, tadalafil 5mg tablets (*Cialis*), the licensed formulation, are designated RED-RED (see page 8).**
- **Apixaban (*Eliquis*) is the latest of the newer oral anticoagulants to be recommended by NICE as an option for the prevention of stroke and systemic embolism in people with non-valvular atrial fibrillation. The product is initially designated RED for this indication; local guidance on the use of newer oral anticoagulants within this context is in the process of being updated and will be published soon (see page 9).**
- **PACEF guidance on primary care rebate schemes is published (see page 10).**
- **Prescribers should ensure that patients taking quinine preparations for nocturnal leg cramps are reviewed quarterly with a view to discontinuing therapy if there is no discernible benefit (see page 10).**
- **A Gout Treatment Algorithm is published (see page 12).**

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

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SUMMARY OF PACEF DECISIONS: *APRIL 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Apixaban (*Eliquis*) tablets 2.5mg and 5mg	For the prophylaxis of venous thromboembolism in adults after hip or knee replacement surgery	RED Approved for Joint Formulary for this indication
Apixaban (*Eliquis*) tablets 2.5mg and 5mg	For the prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one risk factor	RED subject to review Approved for Joint Formulary for this indication
Aquamax Emollient Cream (SLS free)	For use in eczema, psoriasis and other dry skin conditions.	GREEN
Epoetin alfa prefilled syringe (*Eprex*)	Licensed for the treatment of symptomatic anaemia associated with chronic renal failure in patients on dialysis and for symptomatic anaemia associated with chronic renal failure for patients not yet on dialysis	AMBER Shared care guideline available Approved for Joint Formulary for this indication
Epoetin beta prefilled syringe (*NeoRecormon*)	Licensed for the treatment of symptomatic anaemia associated with chronic renal failure in patients on dialysis and for symptomatic anaemia associated with chronic renal failure for patients not yet on dialysis	AMBER Shared care guideline available. Approved for Joint Formulary for this indication
Darbepoetin alfa prefilled syringe (*Aranesp*)	Licensed for the treatment of symptomatic anaemia associated with chronic renal failure in patients	AMBER Shared care guideline available. Approved for Joint Formulary for this

	on dialysis and for symptomatic anaemia associated with chronic renal failure for patients not yet on dialysis	indication
Fluocinolone acetonide intravitreal implant (*Iluvien*) 190 microgram	Licensed for the treatment of vision impairment associated with chronic diabetic macular oedema considered insufficiently responsive to available therapies	RED-RED Not approved for Joint Formulary for this indication
Midodrine 2.5mg and 5m g tablets (*Gutron*)	For the treatment of idiopathic orthostatic hypotension and vasovagal syncope	AMBER Shared care guideline available Approved for Joint Formulary for this indication
Pioglitazone 15mg / Metformin 850mg tablets (*Competact*)	Second line treatment of type 2 diabetes, particularly in overweight patients, inadequately controlled by maximal tolerated doses of metformin.	RED-RED for new patients. All existing patients on Competact should be reviewed with a view to prescribing constituent components separately in the future.
Ranibizumab (*Lucentis*) intravitreal injection	For the treatment of visual impairment due to diabetic macular oedema in adults	RED Within NICE criteria Approved for Joint Formulary for this indication
Rifaximin tablets 550mg (*Targaxan*)	For the reduction in recurrence of overt hepatic encephalopathy	AMBER Approved for Joint Formulary for this indication
Rifaximin tablets 200mg (*Xifaxanta*)	For non-invasive traveller's diarrhoea	RED-RED Not approved for Joint Formulary for this indication
Tadalafil 5mg tablets (*Cialis*)	Licensed for the treatment of benign prostatic hypertrophy	RED-RED NB NICE are due to publish an edition of *Evidence Summary: New Medicines* on tadalifil for this indication shortly. This decision will be reviewed once the NICE ESNM is published. Not approved for Joint Formulary for this indication
Tadalafil 2.5mg, 5mg, 10mg and 20mg tablets (*Cialis*)	Licensed for the treatment of erectile dysfunction	GREEN Second line option after sildenafil (*Viagra*). *Viagra* patent expiry is due in June 2013. Approved for Joint Formulary for this indication
Tapentadol sustained release tablets 50mg, 100mg, 150mg, 200mg, 250mg (*Palexia SR*)	For severe chronic pain	RED-RED
Vinflunine intravenous infusion (*Javlor*)	Licensed as monotherapy for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a platinum containing regimen	RED-RED Not approved for Joint Formulary for this indication

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 in Lincolnshire website (www.lincolnshire.nhs.uk). Follow the commissioning link to PACEF.

PATENT EXPIRY: *SILDENAFIL 25MG, 50MG AND 100MG TABLETS (VIAGRA)*

The next high profile patent expiry to impact on primary care will be the expiry of the *Viagra* (sildenafil) patent in June 2013. In preparation for this, practices are urged to ensure that all sildenafil prescribing is by brand name. Potential savings from the patent expiry have been calculated and reported in the QIPP savings data recently circulated to all four Lincolnshire CCGs. Across Lincolnshire, if the sildenafil generic price falls to half the *Viagra* price (a conservative estimate) the potential saving will be over £500,000pa. Increasing the proportion of patients receiving generic sildenafil as the phosphodiesterase type-5 (PDE5) inhibitor of choice (currently 41%) will increase this saving still further.

There are no comparative studies between the three oral PDE5 inhibitors that are available in the UK. A systematic review published in 2009 found no difference between the drugs in terms of efficacy and adverse effects. However, there are differences between the agents in terms of how they are taken and their licensed indications. Tadalfil (*Cialis*) has a longer serum half-life than alternative agents and thus has a longer duration of action (up to 36 hours compared to 4 to 5 hours with sildenafil). While this may be beneficial in some patients, it is unlikely to be necessary for all of those currently prescribed tadalafil in county. The significant cost differential that will imminently open up between generic sildenafil tablets and tadalafil 10mg/20mg (*Cialis*) will necessitate review of these patients. The sildenafil patent expiry also offers an opportunity to review all patients on once daily tadalafil 2.5mg or 5mg tablets (*Cialis*). This is an exceptionally high cost intervention that was assessed in *PACE Bulletin* Vol 3 No 4 (April 2009) and found to be only cost-effective in patients anticipating sexual activity at least twice weekly. The emergence of low cost generic sildenafil will change the terms of this cost-effectiveness assessment and will necessitate re-assessment of this product.

PACEF Recommendation:

Prescribers should ensure that generic sildenafil tablets are used as the first line PDE5 inhibitor of choice for the treatment of erectile dysfunction. All remaining branded prescribing of *Viagra* should be switched to generic sildenafil. Existing patients taking alternative branded PDE5 inhibitors (tadalafil (*Cialis*) and vardenafil (*Levitra*)) should be reviewed at their next appointment with a view to ensuring that sildenafil naïve patients are switched to sildenafil where appropriate. Prescribing of once daily tadalafil 2.5mg and 5mg tablets (*Cialis*) will also need to be reviewed within the context of the emergence of significantly lower cost therapy.

Prescribers are reminded that PDE5 inhibitors should only be prescribed on the NHS to treat ED in men who: (1) have diabetes, multiple sclerosis, Parkinson's disease, poliomyelitis, prostate cancer, severe pelvic injury, single gene neurological disease, spina bifida or spinal cord surgery; (2) are receiving dialysis for renal failure; (3) have had radical pelvic surgery, prostatectomy (including transurethral resection of the prostate) or kidney transplant. Additional arrangements are in place to treat those suffering severe distress as a result of impotence, although the *BNF* specifies that prescribing should be from specialist centres only. All prescriptions should be marked 'SLS'. In terms of recommended quantities, one treatment a week is considered appropriate for most patients, although a GP may prescribe more at his/her discretion. Private prescribing is advised for patients who require a PDE5 inhibitor to treat ED, but who do not qualify for NHS treatment as defined above.

REVIEW: PIOGLITAZONE 15MG / METFORMIN 850MG TABLETS (COMPETACT)

Pioglitazone is the last of the thiazolidinedione or glitazone anti-diabetic drugs available in the UK. It is licensed for the second or third line treatment of type 2 diabetes mellitus either alone or in combination with metformin, a sulfonylurea or insulin. Following the patent expiry of *Actos* in January 2011, generic pioglitazone became available and the price gradually fell from over £30 per month to less than £4 (see cost comparison). Unfortunately, the price of the pioglitazone 15mg/metformin 850mg combination product (*Competact*) has failed to keep in step with the generic components and is now substantially more expensive that the two components prescribed separately.

	Pack	Drug Tariff April 13
Pioglitazone 15mg tablets	28	£2.86
Pioglitazone 30mg tablets	28	£3.88
Pioglitazone 45mg tablets	28	£4.75
Pioglitazone 15mg / Metformin 850mg tablets (*Competact*)	**56**	**£35.89**
Metformin 850mg tablets	56	£1.20

Although pioglitazone use is in gradual decline, expenditure within Lincolnshire remains in excess of £0.5M pa. Moving from *Competact* to the separate components is likely to generate savings of £30 per patient per month or £400 per patient per year. Applied across Lincolnshire, such a change could generate efficiency savings in excess of £320,000pa. This saving is quantified at practice, locality and CCG level in QIPP savings data recently circulated to all four CCGs.

PACEF Recommendation:
Pioglitazone 15mg/metformin 850mg tablets (*Competact*) are significantly over-priced in relation to the generically available separate components, metformin 850mg tablets and pioglitazone tablets. All existing patients on *Competact* should be reviewed with a view to prescribing constituent components separately in the future. There should be no new initiations of *Competact* which is now designated RED-RED for new patients.

REVIEW: *TAPENTADOL PROLONGED RELEASE TABLETS (PALEXIA SR)*

Tapentadol is an opioid analgesic combining two mechanisms of action: mu-opioid receptor agonism and noradrenaline reuptake inhibition. The prolonged-release tablets (Palexia SR) are licensed for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics. The immediate-release tablets (Palexia) are licensed for the relief of moderate to severe acute pain in adults.

The efficacy of tapentadol prolonged-release has been assessed in osteoarthritis, lower-back and diabetic neuropathic pain. Tapentadol is significantly more effective than placebo in reducing average pain intensity, and non-inferior to oxycodone controlled-release. Tapentadol has not been compared with opioid analgesics other than oxycodone and it has not been studied in cancer pain. The incidence of gastro-intestinal adverse effects is less common with tapentadol than with oxycodone.

There is no published comparative data between tapentadol and any other opioid analgesic other than oxycodone. Tapentadol has been studied in cancer pain, but much of the preliminary data has only been presented at international conferences and has yet to be published. Early signs suggest that there may be a role in the

management of moderate to severe chronic cancer pain, but further studies are required for a proper evaluation.

A cost comparison with oxycodone modified release (*Oxycontin* and *Longtec*) reveals that the recently launched lower cost *Longtec* preparation provides a lower cost alternative at most equivalent strengths. Tapentadol SR 50mg is equivalent to oxycodone CR 10mg.

Drug	Dose	Cost
Tapentadol sustained release tablets 50mg (*Palexia SR*)	50mg twice daily	£24.91
Tapentadol sustained release tablets 100mg (*Palexia SR*)	100mg twice daily	£49.82
Tapentadol sustained release tablets 150mg (*Palexia SR*)	150mg twice daily	£74.73
Tapentadol sustained release tablets 200mg (*Palexia SR*)	200mg twice daily	£99.64
Tapentadol sustained release tablets 250mg (*Palexia SR*)	250mg twice daily	£124.55
Oxycodone prolonged release tablets 5mg (*Longtec*)	5mg every 12 hours	£20.00 (2x28's)
Oxycodone prolonged release tablets 10mg (*Longtec*)	10mg every 12 hours	£19.99
Oxycodone prolonged release tablets 20mg (*Longtec*)	20mg every 12 hours	£39.98
Oxycodone prolonged release tablets 40mg (*Longtec*)	40mg every 12 hours	£79.98
Oxycodone prolonged release tablets 80mg (*Longtec*)	80mg every 12 hours	£159.98
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

MIMS May 2013

PACEF Recommendation:
PACEF last reviewed tapentadol (*PalexialPalexia SR*) in February 2012. In that review, it was acknowledged that the drug emerged as non-inferior to oxycodone in trials and was better tolerated in terms of fewer gastrointestinal side effects. Nonetheless, comparative data against a number of potential alternatives, such as modified release morphine, is still lacking. Additionally, the launch of the lower cost oxycodone modified release preparation, *Longtec*, has resulted in an oxycodone product becoming available that is lower cost than tapentadol PR at equivalent strength. As a result of this tapentadol prolonged release tablets (*Palexia SR*) continue to be designated RED-RED.

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NEW DRUG ASSESSMENT: *RIFAXIMIN 550MG TABLETS (TARGAXAN)*

Rifaximin (*Targaxan*) is a semi-synthetic derivative of the antibiotic rifamycin licensed for the reduction in recurrence of overt hepatic encephalopathy. 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 £259.23 per month which is slightly lower in cost that rifaximin (*Xifaxanta*), an unlicensed equivalent that was previously approved by PACEF for this indication (see *PACE Bulletin* Volume 6 No 19 (December 2012).

PACEF Recommendation:
Rifaximin tablets 550mg (*Targaxan*) 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*) should no longer be used for this indication as they do not hold a marketing authorisation for the treatment of hepatic encephalopathy and a licensed equivalent is now available. Existing patients taking unlicensed *Xifaxanta* for the treatment of hepatic encephalopathy should be reviewed at their next appointment with a view to transferring them to the licensed product. Rifaximin tablets 200mg (*Xifaxanta*) continue to be designated RED-RED for the treatment of non-invasive travellers' diarrhoea.

SHARED CARE GUIDELINES

PACEF have reviewed and approved the following Shared Care Guidelines:

- *Midodrine for the treatment of Orthostatic Hypotension and Vasovagal Syncope* (March 2013)
- *Erythropoiesis Stimulating Agents (ESA's) in the treatment of Anaemia of Chronic Kidney Disease: Epoetin Beta (NeoRecormon®), Darbepoetin alfa (Aranesp®), Epoetin Alfa (Eprex®)* (March 2013)

Copies of the guidelines are all available through the NHS in Lincolnshire website (www.lincolnshire .nhs.uk). Specific queries should be addressed to Cathy Johnson, Interface Lead Pharmacist, GEM Commissioning Support Unit (email address: Cathy.Johnson@GEMCSU.nhs.uk).

NICE TECHNOLOGY APPRAISAL 271: *FLUOCINOLONE ACETONIDE INTRAVITREAL IMPLANT FOR THE TREATMENT OF CHRONIC DIABETIC*

***MACULAR OEDEMA AFTER AN INADEQUATE RESPONSE TO PRIOR THERAPY* (JANUARY 2013)**

Fluocinolone acetonide intravitreal implant is **not recommended** for the treatment of chronic diabetic macular oedema considered insufficiently responsive to available therapies.

PACEF Recommendation:
Fluocinolone acetonide intravitreal implant (*Iluvien*) is not approved for this indication and is designated RED-RED.

NICE TECHNOLOGY APPRAISAL 272: *VINFLUNINE FOR THE TREATMENT OF ADVANCED OR METASTATIC TRANSITIONAL CELL CARCINOMA OF THE UROTHELIAL TRACT* (JANUARY 2013)

Vinflunine is **not recommended** within its marketing authorisation for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract that has progressed after treatment with platinum-based chemotherapy.

PACEF Recommendation:
Vinflunine intravenous infusion (*Javlor*) is designated RED-RED for this indication.

NICE TECHNOLOGY APPRAISAL 273: *TADALAFIL FOR THE TREATMENT OF SYMPTOMS ASSOCIATED WITH BENIGN PROSTATIC HYPERPLASIA* (TERMINATED APPRAISAL) (JANUARY 2013)

NICE is unable to recommend the use in the NHS of tadalafil (*Cialis*) for the treatment of symptoms associated with benign prostatic hyperplasia because the manufacturer (Lilly) were unable to compile sufficient evidence to estimate the cost-effectiveness of the product within the defined treatment pathway (i.e. management of lower urinary tract symptoms in men).

PACEF Recommendation:
Tadalafil 5mg tablets (*Cialis*) are the only strength of tadalafil licensed for the treatment of benign prostatic hypertrophy; they are now designated RED-RED for this indication. Tadalafil 2.5mg, 5mg, 10mg and 20mg tablets (*Cialis*) continue to be approved for use in erectile dysfunction; designation GREEN. In view of the patent expiry of sildenafil (*Viagra*) in June 2013, tadalafil should increasingly be seen as a second line treatment option for erectile dysfunction.

NICE TECHNOLOGY APPRAISAL 274: *RANIBIZUMAB FOR TREATING DIABETIC MACULAR OEDEMA* (RAPID REVIEW OF TECHNOLOGY APPRAISAL GUIDANCE 237) (FEBRUARY 2013)

Ranubizumab is recommended as an option for treating visual impairment due to diabetic macular oedema only if:

- the eye has a central retinal thickness of 400 micrometres or more at the start of treatment and
- the manufacturer provides ranibizumab with the discount agreed in the patient access scheme.

Ranibizumab (*Lucentis*) intravitreal injection blocks the action of vascular endothelial growth factor A (VEGF-A). In diabetic macular oedema, VEGF-A causes blood vessels to leak in the macula, the area of the retina responsible for the clearest vision. By inhibiting the action of VEGF-A, ranibizumab reduces oedema and limits visual loss or improves vision. It is administered as a single intravitreal injection of 0.5mg. The treatment is given monthly and continued until maximum visual acuity is reached and has been maintained for 3 months. This is a reassessment of ranibizumab for this indication; earlier guidance from NICE published in NICE TA 237 (November 2011) did not recommend its use within this context. NICE have now reassessed the product and have concluded that treatment is cost-effective for a sub-group of people with thicker retinas (i.e. 400 micrometres or more).

PACEF Recommendation

Ranibizumab (*Lucentis*) intravitreal injection is re-designated RED for the treatment of visual impairment due to diabetic macular oedema in adults within NICE criteria. This is a change from the previous RED-RED classification.

NICE TECHNOLOGY APPRAISAL 275: *APIXABAN FOR PREVENTING STROKE AND SYSTEMIC EMBOLISM IN PEOPLE WITH NONVALVULAR ATRIAL FIBRILLATION* (FEBRUARY 2013)

Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:

- prior stroke or transient ischaemic attack.
- age 75 years or older.
- hypertension.
- diabetes mellitus
- symptomatic heart failure.

The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of INR control.

PACEF Recommendation:

PACEF issued comprehensive guidance on the use of warfarin, dabigatran and rivaroxaban for the prevention of stroke and systemic embolism in atrial fibrillation in *PACE Bulletin* Vol 6 No 13 (August 2012). Both dabigatran (*Pradaxa*) and rivaroxaban (*Xarelto*) are approved for use for this indication by NICE and are designated GREEN. A second edition of that guidance is in preparation in consultation with colleagues from ULH that will include apixaban (*Eliquis*). Pending the publication of further guidance, apixaban (*Eliquis*) tablets 2.5mg and 5mg are designated RED for this indication and are approved for use within the Joint Formulary. Further guidance will be published shortly.

PACEF GUIDANCE ON PRIMARY CARE REBATE SCHEMES

An increasing number of pharmaceutical companies are offering rebates against the NHS reimbursement price of some of their products; such rebates are tempting to CCGs as they may help to aid the delivery of financial balance. There has been considerable interest in these schemes within primary care with at least one-third of PCTs admitting to claiming rebates when surveyed.

Having reviewed this issue, PACEF have concluded that the evaluation of these schemes should not be part of the core PACEF function. Our intention is to keep the processes of new drug assessment and rebate scheme evaluation separate in order to preserve the integrity of our local decision making. Once a PACEF decision on a product has been made, the evaluation of the relevant rebate scheme (where available) can be made outside of PACEF subject to the views of the individual CCG. Cathy Johnson and Stephen Gibson are entirely happy to work with any or all of the Lincolnshire CCGs to evaluate specific schemes that are of interest.

There are clearly commercial reasons why big pharmaceutical companies are offering rebates as keenly as they are. Many of the schemes specify regular formal review and are conditional on market share growth for the product(s) linked to the scheme. Regular quarterly contact with CCG officers and members of the prescribing team is worth quite a lot to big pharmaceutical company with or without (but preferably with) market share growth. Dept of Health advice is not to participate in such schemes as they undermine nationally negotiated pricing agreements.

Please contact either Cathy Johnson or Stephen Gibson if you wish to discuss a particular scheme further or need any help evaluating a scheme or scheme(s).

MHRA DRUG SAFETY UPDATE REMINDER: *QUININE FOR THE MANAGEMENT OF NOCTURNAL LEG CRAMPS*

In June 2010 the MHRA issued advice highlighting the relatively poor evidence base and potential toxicity of quinine for the management of nocturnal leg cramps. Their advice to healthcare professional was a follows:

- Quinine is not a routine treatment for nocturnal leg cramps, and should only be used when cramps regularly disrupt sleep.
- Before use of quinine for nocturnal leg cramps, the risks should be carefully considered relative to the potential benefits
- After a trial of at least 4 weeks, treatment should be stopped if there is no benefit. If treatment continues, the benefits should be assessed around every 3 months
- Patients should be warned not to exceed the recommended dose. Serious side effects including irreversible blindness and death may occur with overdose
- Thrombocytopenia is a rare but potentially life-threatening adverse reaction associated with quinine. Patients should be instructed to stop treatment and consult a physician if signs of thrombocytopenia occur, such as unexplained petechiae, bruising, or bleeding
- Quinine should not be prescribed or given to patients who have previously experienced any adverse reaction to quinine, including that found in beverages.

Since this advice was issued there has not been a significant change in the volume of use of quinine in the Lincolnshire CCGs. Quinine preparations are low cost but reducing the volume of use of these agents where appropriate would potentially reduce toxicity and polypharmacy and the associated tablet burden.

PACEF Recommendation:
Prescribers should ensure that patients taking quinine preparations for nocturnal leg cramps are reviewed quarterly with a view to discontinuing therapy if there is no discernible benefit. Discontinuing inappropriate, ineffective and potentially toxic therapy can help to improve patient safety and reduce the tablet burden in patients on concurrent therapy.

MHRA *DRUG SAFETY UPDATE* (MARCH 2013)

Dabigatran (Pradaxa) is now contraindicated in patients with prosthetic heart valves requiring anti-coagulant treatment because of the risk of thrombosis and haemorrhage

Dabigatran (*Pradaxa*) is a reversible thrombin inhibitor; it is licensed for primary prevention of venous thromboembolic events in adults who have had elective total hip or knee replacement surgery and for prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation. The RE-ALIGN trial compared dabigatran against warfarin in patients with recent mechanical heart valve replacements. There was a higher frequency of thromboembolic events or bleeding events in those treated with dabigatran regardless of the length of time that had elapsed since the valve implantation. **As a result of this, dabigatran is now contraindicated in patients with prosthetic heart valve(s) requiring anticoagulant treatment related to their valve surgery, regardless of the length of time that has elapsed since valve replacement took place.**

Aqueous cream - risk of skin irritation, particularly in children, due to sodium lauryl sulfate content

The MHRA have released a public assessment report on the risks and benefits of aqueous cream when used in children with eczema. Aqueous cream may cause local skin reactions, such as stinging, burning, itching, and redness, when it is used as a leave-on emollient, particularly in children with atopic eczema. The reactions, which are not generally serious, often occur within 20 minutes of application but can occur later. Reactions may be due to the presence of sodium lauryl sulfate or other ingredients. These reactions are only likely to occur when aqueous cream is being used as a leave on emollient but not when used as a wash product. The difference in the irritation potential in some patients may be related to the contact time with the skin, as soap substitutes are largely removed in the washing process. The MHRA have issued the following advice to healthcare professionals:

- Some patients with eczematous conditions, particularly children, may develop adverse skin reactions if aqueous cream is used as a leave-on emollient, often within 20 minutes of application. These reactions are not generally serious. However, patients and their carers should be warned of this risk during an eczema treatment consultation.
- If a patient reports skin irritation (burning, stinging, itching or redness) after the use of aqueous cream, they should discontinue treatment, and an alternative emollient that does not contain sodium lauryl sulfate (SLS) should be tried.

PACEF Note:
PACEF have recently approved *Aquamax Emollient Cream* for use; this product is SLS free.

GOUT TREATMENT ALGORITHM

During initial assessment of acute gout, please consider risk factors

If unsure of diagnosis please refer to a Rheumatologist

ACUTE TREATMENT
Suppress pain and reduce inflammation until acute flare has subsided.

Please consider the following options

- Colchicine 500 mcg twice daily (usually adequate), increase up to four times daily if required (increased risk of diarrhoea).
- **OR** an NSAID (e.g. naproxen 500mg twice daily or ibuprofen 400mg three times daily). Please consider co-prescribing omeprazole or lansoprazole for gastroprotection.
- **OR** a corticosteroid (intra-articular, particularly if single joint) **OR** oral (e.g. prednisolone 20mg for 3 days, then 15mg for 3 days, then 10mg for 3 days then 5mg for 3 days and stop). Steroids are preferred if there are contraindications to NSAIDs.

Advise the patient to use an ice-pack. Measure serum urate levels and renal function after the attack. Serum urate levels measured during an attack may be lower than usual levels. Gout is part of the metabolic syndrome. Please look for and treat associated conditions such as diabetes, hypertension, hypercholesterolemia and obesity

LONG TERM TREATMENT (DRUG OF CHOICE IS ALLOPURINOL)
Treat to target. Aim for a serum urate of 300µmol/L or less (flare-ups less likely if target achieved)[1]
(1). **Consider allopurinol 100mg daily.** Repeat serum urate levels every 2 to 4 weeks and increase dose by 100mg up to 900mg daily in single or divided doses until target urate levels are reached. Most patients will require about 300mg of allopurinol daily[2]
(2). Prophylaxis is required during the initial period of therapy in view of the increased risk of flare. Consider an NSAID (see above) or Colchicine 500 mcg twice daily. Prophylaxis should continue until the target urate level is reached (maximum period of six months)[2]
(3) Dietary advice.
(4) Allopurinol should be used with caution in patients with renal impairment. In moderate renal impairment (eGFR 30-50) use lower doses (maximum 100mg daily) and monitor renal function. Avoid using allopurinol in patients with severe renal impairment (e-GFR less than 30). The risk of hypersensitivity reaction to allopurinol is increased in renal impairment.

ALLOPURINOL SENSITIVITY or CONTRAINDICATION
Treat to target. Aim for a serum urate of 300µmol/L or less (flare-ups less likely if target achieved).
Consider febuxostat 80mg daily; monitor serum urate levels and LFTs at least monthly for the first 6 months and reduce frequency of monitoring afterwards. Febuxostat 80mg is usually adequate but if target is not reached increase to 120mg daily[3].
Febuxostat is not recommended in patients with heart failure and ischaemic heart disease [3]
Febuxostat should be avoided in patients with severe renal impairment (eGFR less than 30). In renal impairment, febuxostat has an advantage over allopurinol because it is processed primarily by the liver and lowering of dose is not usually required. Renal monitoring is essential.

If febuxostat is contraindicated other options include benzbromarone (secondary care only). Please refer complex cases to a Rheumatology clinic. Sulfinpyrazone and probenecid can also be considered.

Gout flares while taking sUA lowering therapy → Suppress pain and reduce inflammation. Do not interrupt allopurinol or febuxostat therapy unless there is a clinical reason.

*Steroids or colchicine are preferable treatments for patients who have concomitant conditions and who are taking medications that contraindicate the use of NSAIDs (e.g warfarin) but they should be used with caution.

References
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2. Rider TG, Jordan KM The modern management of gout. *Rheumatology* (Oxford) 49; 5-14.
3. NICE Technology Appraisal 164 *Febuxostat for the management of hyperuricaemia in people with gout* (December 2008)

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