Lincolnshire NHS

Prescribing and Clinical Effectiveness Bulletin

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MERRY CHRISTMAS AND A HAPPY NEW YEAR TO ALL OUR READERS

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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. Steps will be taken to ensure the widest possible distribution across Lincolnshire PCT and within United Lincolnshire Hospitals Trust and Lincolnshire Partnership Trust. Both paper and electronic copies will be circulated initially with a view to evolving into complete electronic distribution as soon as we are confident that all key stakeholders can access E-mail. There are also plans to make all bulletins, guidelines, formularies, new product assessments, care pathways and other PACEF publications available through the LPCT website.

SUMMARY OF PACEF DECISIONS: DECEMBER UPDATE

Drug	Indication	Traffic Light Status
Adalimumab (Humira)	Moderate to severe active rheumatoid arthritis when response to other disease modifying anti-rheumatic drugs (DMARDs) has been inadequate	RED
Aliskiren (Rasilez)	Treatment of essential hypertension	AMBER Should only be initiated on specialist advice; no shared care guideline required
Bortezomib (Velcade)	Treatment of progressive multiple myeloma	RED
Etanercept (Enbrel)	Moderate to severe active rheumatoid arthritis when response to other disease	RED

	modifying anti-rheumatic drugs (DMARDs) has been inadequate	
Glucosamine hydrochloride (Alateris)	Relief of symptoms in mild to moderate osteoarthritis of the knee	RED-RED Where glucosamine is indicated, 1500mg daily of glucosamine sulphate should be prescribed. Generic glucosamine sulphate or low-cost brands such as Valupak or Natrahealth should be used.
Human Papillomavirus Vaccine (Cervarix and Gardasil)	Prevention of high-grade intraepithelial neoplasia and cervical cancer causally related to HPV types 16 and 18.	RED-RED
Infliximab (Remicade)	Severe active rheumatoid arthritis when response to other disease modifying anti-rheumatic drugs (DMARDs) has been inadequate	RED
Rotigotine transdermal patch (Neupro)	Licensed as monotherapy for the treatment of the signs and symptoms of early stage idiopathic Parkinson's disease and as an adjunct to levodopa with a dopa-decarboxylase inhibitor.	AMBER Should only be initiated on specialist advice; no shared care guideline required

RED-RED: This signifies that a product is **not recommended** for prescribing in **both** primary and 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 ULHT and/or LPT **only** and has **no role in primary 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; in the coming months PACEF will be working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care**. Specialist initiation and shared care guidelines are not considered necessary.

NEW DRUG ASSESSMENTS

ALISKIREN (RASILEZ)

Aliskiren is the first of a potentially new class of oral antihypertensive agents known as renin inhibitors. It is licensed for the treatment of essential hypertension and can be used either as monotherapy or in combination with other antihypertensive agents. Renin catalyses the first step of the Renin Angiotensin System (RAS) by breaking down angiotensinogen. Renin inhibitors bind to renin thus interfering with the RAS and reducing the production of angiotensin-I and the potent vasoconstrictor angiotensin-II from angiotensinogen. Other antihypertensive agents that achieve some or all of their effects through modification of the RAS include beta-blockers (that reduce renin secretion by the kidney), Angiotensin Converting Enzyme

Inhibitors (ACEIs) (which block the conversion of angiotensin-I to angiotensin-II) and angiotensin receptor blocking agents (ARBs) (which block angiotensin receptors).

Most of the published studies were short-term four or eight week trials that compared aliskiren with a thiazide or an ARB. Published data suggests that the short-term antihypertensive effect of aliskiren is at least comparable to existing antihypertensive drugs, although monotherapy comparative data against thiazide diuretics and calcium channel blockers is lacking. Published data also suggest a flat dose-response curve: 600mg daily is no more effective than 300mg daily. Better established alternative antihypertensive agents are linked to long-term cardiovascular outcome studies that confirm benefits in terms of improvements in cardiovascular outcomes. No such data is currently available for aliskiren.

The most common adverse effects with aliskiren reported in trials are headache, dizziness, fatigue and gastro-intestinal disorders; the most common adverse effect is diarrhoea. Aliskiren is associated with a lower incidence of cough than ramipril, although study drop-out rates due to adverse events appear similar between aliskiren and ramipril. The incidence of cough with aliskiren is similar to placebo. Hyperkalaemia may be a concern in combination with other drugs inhibiting the RAS (including ACEIs and ARBs) and in those with reduced kidney function and/or diabetes mellitus.

From this cost comparison below aliskiren emerges as more expensive than any other class of antihypertensive agents; it is comparable in cost to a higher dose of an expensive branded ARB like valsartan.

Drug	**Daily dose range**	**Annual Cost (£)pa**
Aliskiren tablets (Rasilez)	**150mg to 300mg once daily**	**£257.40 to £309.40**
Ramipril capsules (generic)	2.5mg to 5mg once daily	£10.40 to £13.39
Lisinopril tablets (generic)	10mg to 20mg once daily	£9.62 to £17.42
Candesartan tablets (Amias)	8mg once daily	£128.57
Irbesartan tablets (Aprovel)	150mg to 300mg	£163.41 to £219.83
Valsartan capsules (Diovan)	80mg to 160mg once daily	£213.72 to £281.58
Bendroflumethiazide tablets (generic)	2.5mg each morning	£5.59
Amlodipine tablets (generic)	5mg to 10mg daily	£15.21 to £18.59

PACEF Recommendation:
Most of the published data relating to aliskiren is from short-term trials that reveal nothing about long-term efficacy, long-term safety, cost-effectiveness or impact on cardiovascular outcomes. Nonetheless, aliskiren may have a role in patients intolerant to or unresponsive to standard therapies. The number of unanswered questions and the prohibitive comparative cost necessitates that aliskiren should be confined to patients with multiple intolerance to other antihypertensive medications or resistant hypertension. PACEF designation: AMBER. Aliskiren is only appropriate in a small number of carefully selected patients on the advice of a specialist. GPs can initiate following specialist recommendation; no shared care guideline is required.

ROTIGOTINE TRANSDERMAL PATCH (NEUPRO)

Rotigotine is a dopamine receptor agonist formulated as a transdermal patch and licensed as monotherapy for the treatment of the signs and symptoms of early stage

idiopathic Parkinson's disease and as an adjunct to levodopa with a dopa-decarboxylase inhibitor. Supporting evidence derives from small scale trials, not all of which have been published. Studies show significant benefits over placebo relating to the use of rotigotine in the improvement of motor function in early disease and reduction of the period of "off time" in more advanced disease. In a comparative trial with pramipexole, rotigotine was shown to be effective in reducing the number of patients who woke in the "off state".

NICE Clinical Guideline 35, *Parkinson's disease: Diagnosis and management in primary and secondary care* (June 2006), recommends non-ergot dopamine agonists (such as pramipexole, ropinirole, rotigotine) as part of a range of possible first line choices in both early onset Parkinson's disease and as adjunct therapy in advanced disease. Due to the idiosyncratic nature of the underlying condition and differences in individual response to therapy, NICE do not provide specific recommendations as to first line product choice.

Particular tolerability issues identified with rotigotine include a high incidence of site application reactions and an increased incidence of nausea and vomiting. The backing layer of the patch contains aluminium and there is a risk of the patient receiving burns if the patch is not removed prior to MRI scans and cardioversion. Cost comparison is difficult due to the wide range of doses used. Non-ergot derived dopamine agonists are more expensive than alternative therapies, but rotigotine is currently priced comparably with other non-ergot derived alternatives such as ropinirole and pramipexole.

PACEF Recommendation:
Rotigotine transdermal patches are designated AMBER. They are approved for use in primary care following specialist diagnosis in line with the recommendations for the management of Parkinson's disease in NICE Clinical Guideline 35. No shared care guideline is required. Specifically, rotigotine patches should be reserved for second line use in patients who are either experiencing swallowing difficulties, unable to tolerate pramipexole or ropinirole or insufficiently responsive to pramipexole or ropinirole. There may also be a role in those who experience symptoms at night or wake in the 'off' state.

GLUCOSAMINE (ALATERIS)

Glucosamine is a normal constituent of the polysaccharide chains of cartilage and synovial fluid and has a role in maintaining the elasticity, strength and resilience of cartilage. Over the last few years, the medicinal use of glucosamine, obtained either on prescription or purchased from health food stores and pharmacies, has been on the increase. A review of the evidence base for glucosamine undertaken by PACEF revealed the following key points:

(1) The Glucosamine/chondroitin Arthritis Intervention (GAIT) study compared glucosamine sulphate, chondroitin, glucosamine and chondroitin, celecoxib and placebo in 1,583 patients with osteoarthritis of the knee. The dose of glucosamine sulphate used was1500mg daily and the primary outcome was a 20% decrease in knee pain from baseline to week 24 with glucosamine. The placebo effect was very large and glucosamine and chondroitin in combination emerged as no better than placebo.

(2) The Cochrane Collaboration have twice reviewed glucosamine (in 1999 and 2005) and have reached different conclusions on each occasion. In 1999,

they concluded from 12 studies that glucosamine sulphate 500mg three times daily was safe and effective in the treatment of OA of the knee, but remained concerned over long-term safety and effectiveness. In 2005, they reviewed 20 studies of glucosamine in OA hip and knee and were more sceptical, concluding that glucosamine showed no appreciable benefit over placebo.

(3) A Bandolier meta-analysis recently concluded that glucosamine sulphate 1500mg daily could benefit as many as 1 in 5 patients with OA of the knee and calculated a Number Needed to Treat (NNT) of 4.9. An accompanying editorial stressed the relatively small improvements with glucosamine in comparison to other interventions, the importance of individual patient perception and experience, the poor design of many of the published trials and the difficulties in assessing the clinical effectiveness of interventions like glucosamine from such evidence.

(4) The draft NICE Clinical Guideline entitled *Osteoarthritis: the care and management of osteoarthritis in adults* (July 2007) recommends the consideration of glucosamine sulphate 1500mg daily as an adjunct to core treatment for the symptom relief of OA of the knee.

(5) The most common adverse reactions associated with glucosamine are nausea, abdominal pain, indigestion, diarrhoea, constipation, headache and tiredness; all reported adverse reactions are usually mild and transitory.

Alateris is the first licensed formulation of glucosamine; it is licensed for the relief of symptoms in mild to moderate OA of the knee. All other formulations of glucosamine are classified as food supplements and do not have to comply with any pharmaceutical standards. Each tablet contains 625mg of glucosamine hydrochloride; the recommended dose is two tablets (1250mg) once daily. There is very little specific evidence available to justify the use of glucosamine hydrochloride as an alternative to the already established glucosamine sulphate. All of the major research detailed above refers to glucosamine sulphate.

Compared to commonly prescribed alternatives, glucosamine hydrochloride (Alateris) is comparable in cost to a branded coxib. Alternative glucosamine formulations, although unlicensed, contain glucosamine sulphate, the salt utilized in many of the key studies; comparative prices are also much lower than Alateris:

Drug	Daily dose range	Cost	
		3 months	Per annum
Glucosamine (Alateris)	**1250mg**	**£51.52**	**£223.25**
Glucosamine (Valupak®)	1500mg	£6.36	£27.56
Glucosamine (Natrahealth®)	1500mg	£6.39	£27.69
Glucosamine (Lifespan®)	1500mg	£7.74	£33.54
Paracetamol tablets	4g	£6.62	£28.68
Ibuprofen tablets	1200 - 1600mg	£7.20 - 9.60	£31.20- 41.60
Diclofenac	75mg - 150mg	£3.60- 6.09	£15.60 - 26.39
Celecoxib	200mg	£60.33	£261.43
Ibuprofen gel 5%	50g/mth	£7.38	£31.98
Diclofenac gel 1%	100g/mth	£21.00	£91.00

PACEF Recommendation:

The evidence base in support of glucosamine is relatively weak and often conflicted. Nonetheless, there is some evidence of benefit linked to the use of glucosamine sulphate 1500mg daily in the symptomatic relief of osteoarthritis

of the knee. Current evidence also suggests that glucosamine sulphate has a better safety profile than alternatives (for example, NSAIDs), although long-term safety data is lacking. PACEF remain unconvinced that the potential benefits of glucosamine sulphate 1500mg daily can be extrapolated to glucosamine hydrochloride 1250mg daily (Alateris); the premium price of the Alateris formulation in comparison to generic glucosamine sulphate and low cost branded formulations also caused concern. As a result of this, glucosamine hydrochloride 625mg tablets (Alateris) are designated RED-RED. Prescribers wishing to utilize glucosamine sulphate for symptomatic relief of OA of the knee should advise patients to purchase supplies either from their local health food store or community pharmacy. If a prescription for glucosamine sulphate is thought to be indicated, either generic glucosamine sulphate 1500mg daily or a low-cost brand such as Valupak or Natrahealth should be prescribed. Draft guidance from NICE supports the use of glucosamine sulphate in this context, but does not endorse the use of glucosamine and chondroitin combination products

HUMAN PAPILLOMAVIRUS VACCINE (CERVARIX AND GARDASIL)

Following the recent launch of a second human papillomavirus vaccine (Cervarix) the following key points from advice issued earlier in the year have been updated and expanded:

- Cervarix is a new human papillomavirus vaccine licensed for the prevention of high-grade intraepithelial neoplasia and cervical cancer causally related to HPV types 16 and 18.
- The primary vaccination series consists of three separate 0.5ml doses administered according to the following schedule: 0, 1 and 6 months. The cost of this three dose course is £241.50 per patient. The Gardasil schedule is 0, 2 and 6 months and the cost is the same.
- There is a clear statement in the Summary of Product Characteristics for both Cervarix and Gardasil that these vaccines should be used **in accordance with official recommendations**. This is can be further defined as in accordance with the recommendations of the Joint Committee on Vaccination and Immunisation (JCVI) and the Dept of Health (DoH).
- There has been a recent announcement from the Dept of Health that HPV vaccine will be introduced into the national immunisation programme in the autumn of 2008. Vaccination is likely to be introduced for girls aged 12 to 13 years. There will also be a two-year catch-up campaign starting in Autumn 2009 for girls aged up to 18 years.
- GPs and their staff are strongly advised not to be drawn into discussions with the sales force of either GlaxoSmithKline or Sanofi Pasteur MSD on a current role for either of these products. Prescribers are reminded that introduction of HPV vaccine in a small number of individuals considered to be at risk will do nothing to affect overall cervical cancer rates.

PACEF Recommendation:
Both Gardasil and Cervarix HPV vaccines are confirmed as RED-RED.
Until the national vaccination programme is launched, prescribers are advised not to prescribe HPV vaccine (Cervarix or Gardasil) for any patient in primary care, either on the NHS or privately. As both vaccines are licensed for use and have not been black-listed by the NHS, a GP would potentially be in breach of their Terms of Service if they offered the vaccine on private prescription. Until there is an NHS approved national vaccination programme, there is no NHS role.

PRODUCT WITHDRAWALS

CO-PROXAMOL REMINDER

As far back as January 2005, the Medicines and Healthcare products Regulatory Agency (MHRA) announced plans for the phased withdrawal of co-proxamol. Patients were given until the end of 2007 to make the transition to a suitable alternative. As we approach the end of the transition period, all patients currently taking co-proxamol should be moved wherever possible to a suitable alternative. Lincolnshire prescribing figures suggest that there are still a significant number of patients in some practices that have yet to make the change. At the end of the year all of the licenses for the currently available products will be cancelled. Meda currently hold a marketing authorisation for Distalgesic and have agreed to continue to market the product for unlicensed supply into the new year and beyond. This may present a solution for a small number of patients unresponsive or intolerant to alternatives, although prescribing will be unlicensed and remain the responsibility of the prescriber.

LUMIRACOXIB (PREXIGE) REMINDER

As you will already be aware, the UK licenses for lumiracoxib (Prexige) were suspended with immediate effect on the 19th of November in response to advice from the Commission of Human Medicines (CHM). The reason for this abrupt suspension was the identification of a link between this NSAID and severe, potentially life threatening hepatotoxicity. All patients prescribed lumiracoxib should have been contacted and advised to stop taking the treatment. The issue of all repeat prescriptions should also have been stopped and all patients flagged for review. The MHRA view on stopping treatment is that ideally this should have been done straight away, especially in symptomatic individuals, but that it would be acceptable to continue treatment until the next convenient appointment if the patient was well and gaining symptomatic relief from their treatment. All practices prescribing lumiracoxib in Lincolnshire have been formally contacted by members of the PCT Prescribing and Medicines Management Team to notify them of the urgency of this withdrawal.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 129: BORTEZOMIB MONOTHERAPY FOR RELAPSED MULTIPLE MYELOMA (OCTOBER 2007)

The key recommendations are as follows:

- Bortezomib monotherapy is recommended as an option for the treatment of progressive multiple myeloma in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation, under the following circumstances: (1) the response to bortezomib is measured using serum M protein after a maximum of 4 cycles of treatment, and treatment is continued only in people who have a complete or partial response (i.e. reduction in serum M protein of 50% or more or, where serum M is not measurable, an appropriate alternative biochemical response) and (2) the manufacturer rebates the full cost of bortezomib for people who, after a maximum of 4 cycles, have less than a partial response (as defined above).
- People currently receiving bortezomib monotherapy who do not meet these criteria should have the option to continue until they or their clinicians consider it appropriate to stop.

PACEF Recommendation:
Bortezomib has been approved for use within United Lincolnshire Hospitals Trust subject to the criteria and rebate scheme specified by NICE; bortezomib is now designated RED.

NICE TECHNOLOGY APPRAISAL 130: ADALIMUMAB, ETANERCEPT AND INFLIXIMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS (OCTOBER 2007)

The key recommendations are as follows:

- The tumour necrosis factor alpha inhibitors (anti-TNFs) adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have **both** of the following characteristics: (1) Active rheumatoid arthritis (RA) (disease activity score (DAS28) above 5.1 on at least 2 occasions one month apart) and (2) Have undergone trials of two disease modifying anti-rheumatic drugs (DMARDs), including methotrexate (MTX)(unless contra-indicated). A trial of a DMARD is defined as 6 months with 2 months at standard dose, unless significant toxicity has limited the dose and duration of treatment.
- Anti TNFs should normally be used in combination with MTX. Where the patient is unresponsive or intolerant to MTX, adalimumab and etanercept may be given as monotherapy.
- Anti TNF treatment should only be continued subject to an adequate response at 6 months following the initiation of therapy (an improvement of the DAS28 of 1.2 points or more).
- Treatment should be monitored no less frequently than 6 monthly. Treatment should be withdrawn if an adequate response is not maintained (an improvement of the DAS28 of 1.2 points or more).
- An alternative anti-TNF can be considered for patients who have to withdraw from treatment due to intolerance before the initial 6-month assessment of efficacy.
- Escalation of the dose beyond the licensed starting dose is not recommended.
- Treatment should normally be initiated with the least expensive drug.
- Anti-TNFs should not be used for severe active and progressive RA in adults not previously treated with MTX or other DMARDs.
- Initiation and follow up should only be undertaken by a specialist rheumatologist.

PACEF Recommendation:
Adalimumab (Humira), etanercept (Enbrel) and infliximab (Remicade) are all designated RED for this indication. At present, no shared care arrangements exist for any of these treatments and there is no expectation of GP involvement. This may be subject to review in the future, although only those drugs administered by sub-cutaneous injection (e.g. adalimumab and etanercept) have any future prospect of shared care.

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