Lincolnshire NHS

Prescribing and Clinical Effectiveness Bulletin

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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: SEPTEMBER UPDATE

(New additions for September are highlighted in **bold**)

Drug	Indication	Traffic Light Status
Eplerenone (Inspra)	**Stable patients with left ventricular dysfunction (LVD) with evidence of heart failure (HF) following myocardial infarction.**	**AMBER (Specialist initiation, but no shared care guideline required)**
Exforge tabs (amlodipine/valsartan)	Hypertension	RED-RED
Human Papillomavirus Vaccine (Gardasil)	Prevention of cervical cancer	RED-RED **(N.B. Prescribers are advised not to prescribe HPV either on the NHS or privately. A national vaccination programme is in development)**
Katya tablets	Oral contraception	GREEN
Lanthanum carbonate tabs (Fosrenol)	Hyperphosphataemia in chronic renal failure	AMBER
Natalizumab inf (Tysabri)	Highly active relapsing remitting multiple sclerosis	RED-RED (N.B. It has been agreed that following the imminent publication of a new NICE

		TA, natalizumab will be reclassified as RED)
Omacor capsules	Hypertriglyceridaemia Secondary prevention after MI	RED-RED
Omalizumab 150mg inj (Xolair)	Severe persistent allergic asthma in patients 12 years and over.	RED-RED Subject to a favourable NICE TA, omalizumab is likely to be re-classified as RED later in the year.
Ranibizumab (Lucentis)	**Treatment of neovascular (wet) age-related macular degeneration (AMD).**	**RED-RED**
Sevelamer tabs (Renagel)	Hyperphosphataemia in chronic renal failure	AMBER
Sunya tablets	Oral contraception	GREEN
Testosterone 2% gel (Tostran)	Testosterone replacement in male hypogonadism with confirmed testosterone deficiency	GREEN
Testosterone patch (Intrinsa)	Women with hypoactive sexual desire disorder	RED-RED
Varenicline (Champix)	**Smoking cessation in adults**	**GREEN** **NB Should be considered as a potential second line alternative to bupropion in patients committed to stopping smoking that have tried and failed to quit using NRT support.**

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.

HUMAN PAPILLOMAVIRUS VACCINE (GARDASIL)

Further advice has been requested on the prescribing of Human Papillomavirus Vaccine (Gardasil). The following key points from advice issued earlier in the year have been updated and expanded:

- Gardasil is licensed for the prevention of high-grade cervical dysplasia, cervical carcinoma, high-grade vulvar dysplastic lesions and external genital warts causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18. The product license is based on efficacy data relating to the use of Gardasil in adult females aged 16 to 26 years and on the demonstration of immunogenicity of Gardasil in 9 to 15 year old children and adolescents.

- The primary vaccination series consists of three separate 0.5ml doses administered according to the following schedule: 0, 2 and 6 months. The cost of this three dose course is £241.50 per patient.
- There is a clear statement in the Summary of Product Characteristics that Gardasil should be used **in accordance with official recommendations**.
- There are, as yet, no official recommendations from the Joint Committee on Vaccination and Immunisation (JCVI) or from the Department of Health on the role of HPV vaccine (Gardasil), although there has been a recent announcement from the Dept of Health that HPV vaccine is likely to be introduced into the national immunisation programme by autumn 2008 (subject to a favourable cost-benefit analysis). Vaccination is likely to be introduced for girls aged around 12 to 13 years; there is some speculation that a further catch-up programme will also be part of the final programme.
- Further details of this vaccination programme will be announced at a national meeting of Vaccination and Immunisation leads in October. A summary of key points from that meeting will appear in the PACE bulletin later in the year.
- GPs and their staff are strongly advised not to be drawn into discussions with the Sanofi Pasteur MSD sales force on a current role for this product. 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

Until the national vaccination programme is launched, prescribers are advised not to prescribe HPV vaccine (Gardasil) for any patient in primary care, either on the NHS or privately. As Gardasil is licensed for use and has 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.

NEW PRODUCTS UPDATE

RANIBIZUMAB INTRAVITREAL INJECTION (LUCENTIS)

Ranibizumab (Lucentis) is a humanised monoclonal antibody fragment licensed for the treatment of neovascular (wet) age-related macular degeneration (AMD). It is a specialist treatment that is initiated with a loading phase of one injection per month for three consecutive months, followed by a maintenance phase in which patients are monitored for visual acuity on a monthly basis. When injected into the eye, it reduces endothelial cell proliferation, vascular leakage and new blood vessel formation. In the MARINA and ANCHOR studies, almost all patients treated with monthly injections of ranibizumab maintained their visual acuity, with approximately 34% to 40% experiencing an improvement in vision. Side effects identified to date relate to the injection procedure itself (e.g. endophthalmitis, retinal tear and intraocular inflammation). The long-term safety of ranibizumab has not been demonstrated beyond two years; there is also limited data on cost-effectiveness. The cost of each injection is £761; for 3 to12 injections per year the annual cost per patient ranges from £2,280 to £9,130. As there are potentially 70 to 100 new cases of wet AMD per year in Lincolnshire the financial impact on the healthcare community could be considerable. NICE recently published an Appraisal Consultation Document that approved ranibizumab for use within the NHS, but restricted treatment to the better-seeing eye in selected patients with predominately classic subfoveal lesions. The resulting controversy and need for revision is likely to delay publication of the Technology Appraisal until 2008.

PACEF Recommendation
As an interim measure, ranibizumab is classified as RED-RED, primarily due to concerns over cost-effectiveness. Further review by the East Midlands Specialized Commissioning Group may result in a change to this position in the coming months. A NICE TA is due for publication in 2008.

EPLERENONE (INSPRA)

Eplerenone (Inspra) is the only aldosterone antagonist licensed for use in stable patients with left ventricular dysfunction (LVD) with evidence of heart failure (HF) following myocardial infarction. PACEF reviewed the evidence for eplerenone on the basis of recent advocacy of the treatment in NICE CG 48, *MI: secondary prevention*. The license for eplerenone is based on the Eplerenone Post Acute MI HF Efficacy Survival Study (EPHESUS), a multicentre, international, randomized, double-blind, placebo controlled trial. 6,632 patients, 3 to 14 days after MI with a left ventricular ejection fraction (LVEF) of ≤40% and clinical symptoms of HF, were randomized to eplerenone 25mg daily initially (titrated up to 50mg daily) or placebo. Both arms received optimal standard care (e.g. ACEI or angiotensin receptor blocker (ARB), beta-blocker (BB), diuretics, aspirin, statin). The results of the study revealed that eplerenone significantly reduced all cause mortality, cardiovascular mortality and hospitalisation for cardiovascular events. The Number Needed to Treat (NNT) to save one life in one year is 50; the one year NNT to prevent one death from CV causes or hospitalisation for CV event is 33. The only other aldosterone antagonist available is spironolactone, but no trial evidence is available to support the post MI LVD indication. Consequently, spironolactone is not licensed post-MI, although it is licensed for the treatment of HF.

NICE have previously recommended that spironolactone may be indicated for patients with HF who remain moderately to severely symptomatic despite optimal treatment with a diuretic, ACEI and BB. Within this context, eplerenone should be reserved for those intolerant to spironolactone. Rates of gynaecomastia, impotence and breast pain with eplerenone are similar to placebo.

PACEF Recommendation:
Eplerenone is approved for use post-MI (initiated within 3 to 14 days of the event) for patients with signs and symptoms of heart failure and left ventricular systolic dysfunction. Specialist diagnosis, initiation and intensive initial monitoring are required; renal function and serum potassium should be monitored before and during treatment. Within this context, eplerenone is classified as AMBER, although the routine nature of continued monitoring in primary care does not necessitate a shared care guideline.
For patients with clinical heart failure and LVSD already taking spironolactone, treatment can be continued post-MI. Eplerenone represents a better tolerated alternative for those unable to tolerate spironolactone. Within this context it could be initiated by a GP.

NICE UPDATES

NICE TECHNOLOGY APPRAISAL 123: *VARENICLINE FOR SMOKING CESSATION*

NICE have endorsed the use of varenicline (Champix) within its licensed indications (smoking cessation in adults) as an option for smokers who have expressed a desire to quit smoking. They recommend that it should normally be prescribed as part of a programme of behavioural support. The published clinical trials comparing varenicline with bupropion and placebo (but not nicotine replacement therapy (NRT)) were reviewed in the February 2007 issue of *Prescribing Link Extra*. From this assessment, it was apparent that varenicline performed well in comparison to bupropion, but the lack of comparative evidence against NRT precluded anything other than cautious endorsement as a third line agent.

The evidence available to NICE beyond that considered earlier in the year is a single unpublished open-label trial (n=957) that compared varenicline with NRT and a Pfizer meta-analysis of 70 NRT trials, 12 bupropion trials and 4 varenicline trials. The Pfizer meta-analysis showed varenicline to be superior to NRT and bupropion at 3 months and 12 months. A Pfizer submitted cost-effectiveness analysis also convinced NICE that varenicline was potentially more cost-effective than NRT and bupropion despite having a higher acquisition cost. From this NICE conclude that:

- Varenicline is superior to NRT and bupropion in achieving continuous abstinence.
- Varenicline represents a cost-effective use of NHS resources.
- Varenicline should normally be provided in conjunction with counselling and support, but if such support is refused or not available, this should not preclude treatment.

The recommended dose of varenicline is 1mg twice daily for 12 weeks; a 12 week course costs £163.80. This can be compared to £55 to £110 for a complete course of NRT patches and approximately £80 for a 9 week course of bupropion. In short, varenicline is approximately twice the cost of alternative smoking cessation support therapies.

PACEF Recommendation:
Varenicline is classified as GREEN. At this stage, it should be considered as a potential second line alternative to bupropion in patients committed to stopping smoking that have tried and failed to quit using NRT support. An assessment of cost-effectiveness based on real patient experience is currently being undertaken by Phoenix and will be used to inform further guidance on varenicline to be issued in the coming months. Any form of pharmacological smoking cessation support should be provided in conjunction with an appropriate level of behavioural support.

NICE CLINICAL GUIDELINE 49: FAECAL INCONTINENCE

A key point summary of the new NICE Clinical Guideline on the management of faecal incontinence (FI) in adults is provided below:

- Utilize the relevant skills, training and experience of staff within an integrated continence service.
- Sensitively screen high-risk groups who may be faecally incontinent but reluctant to admit to it due to social stigma. High-risk groups include: the frail elderly, those with loose stools or diarrhoea from any cause, women following childbirth, people with neurological or spinal disease, severe cognitive impairment, urinary

incontinence, pelvic organ prolapse or rectal prolapse, people who have had colonic resection or anal surgery or undergone pelvic radiotherapy, people with perianal soreness, itching or pain and people with learning disabilites.

- A focused baseline assessment should include relevant medical history, general examination, anorectal examination and a cognitive assessment (if appropriate)
- Underlying problems should be addressed before initial management of faecal incontinence (e.g. faecal loading, treatable causes of diarrhoea, warning signs of lower GI cancer, rectal prolapse or third-degree haemorrhoids, acute anal sphincter injury, acute disc prolapse etc).
- The individual's bowel habit should be addressed aiming for ideal stool consistency and satisfactory bowel emptying at a predictable time.
- If initial management fails consider specialist advice.
- Specialist continence services may include: pelvic floor muscle training, bowel retraining, dietary assessment and management, biofeedback, electrical stimulation and rectal irrigation.
- Advice on long term management and a treatment algorithm is provided.
- If drugs are contributing to FI, consider alternatives.
- Prescribe anti-diarrhoeal drugs for people with loose stools and associated FI once other causes have been excluded. Loperamide is recommended first line; for doses less than 2mg, use loperamide hydrochloride syrup.
- Codeine phosphate or co-phenotrope are suggested as alternatives if the patient is unable to tolerate loperamide.
- Loperamide is not recommended in those with: hard or infrequent stools, acute diarrhoea without diagnosed cause or acute flare-up of ulcerative colitis.
- Initiate loperamide at a low dose and titrate up until desired stool consistency is reached.
- Continence products, disposable body worn pads, bed pads, anal plugs etc may also be required.

Local guidelines on the management of faecal incontinence are in the early stages of development.

ADDENDUM:
NICE CLINICAL GUIDELINE 48 - *MI: SECONDARY PREVENTION*
In Issue 1 Number 3 of the *PACE Bulletin*, generic ramipril capsules were advocated post MI as one of the most cost-effective ACEI formulations currently available. Standard twice daily licensed doses were also quoted. During subsequent discussion at the August PACEF, it was acknowledged that most prescribers prefer to prescribe ramipril once daily. PACEF are fully aware of this and in support of once daily ramipril within this context.

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