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: JULY UPDATE

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

Drug	Indication	Traffic Light Status
Exforge tabs (amlodipine/valsartan)	Hypertension	RED-RED
Human Papillomavirus Vaccine (Gardasil)	Prevention of cervical cancer	RED-RED
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.**
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

RED-RED: This signifies that a product is **not recommended** for prescribing in **both** primary and secondary care.
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 PRODUCTS UPDATE

OMALIZUMAB 150mg INJECTION (XOLAIR)

Omalizumab is a new injectable anti- immunoglobulin E monoclonal antibody licensed for the treatment of severe persistent allergic asthma in patients aged 12 and over. It works by preventing IgE from binding to receptors on mast cells and basophils, thus reducing the amount of free IgE that is available to trigger the allergic cascade. Pooled data from 7 studies, including the pivotal INNOVATE study, has shown a significantly lower annual rate of exacerbations in omalizumab treated patients compared to placebo. However, the economic case for omalizumab has yet to be made; the Scottish Medicines Consortium (SMC) has rejected the drug for use within NHS Scotland due to its high cost and concerns over cost-effectiveness. NICE are currently working on a Technology Appraisal that looks set to make omalizumab available to a tightly defined group of severe asthmatic patients in the future.

PACEF Recommendation:
Omalizumab (Xolair) is classified as RED-RED. It should not be prescribed in either primary or secondary care in Lincolnshire. Subject to a favourable NICE TA, the drug is likely to be re-classified as RED later in the year.

OMEGA-3-ACID ETHYL ESTERS CAPSULES (OMACOR)

Omacor contains a combination of the omega-3 series essential polyunsaturated fatty acids: eicosapentaenoic acid (EPA) and docosahexanenoic acid (DHA). It is licensed as adjuvant therapy in secondary prevention after MI and for hypertriglyceridaemia. It probably exerts its effect post-MI by a combination of anti-arrhythmic, anti-inflammatory and antithrombotic effects and effects on endothelial

dysfunction. The evidence base for Omacor post-MI is largely based around a single trial known as the GISSI Prevenzione study. This was an open-label randomized trial carried out in 11,324 Italian patients who had suffered an MI in the preceding 3 months. Patients were randomized to Omacor one daily; vitamin E 300mg; both or no supplement. The dose of omega-3 fatty acid corresponded to 100g of oily fish per day. The trial was published in 1999 and data collection took place in Italy during the mid to late 90s. During this period, the use of secondary prevention measures widely in use today (e.g. statins, aspirin and beta-blockers) was much lower. Many have speculated that the positive effects of a Mediterranean diet on the trial population in combination with a much lower use of alternative secondary prevention measures is likely to have resulted in the trial over-estimating the benefits of Omacor. The results showed a statistically significant reduction in the primary endpoint of death, non-fatal MI and non-fatal stroke, although the Numbers Needed to Treat (NNT) were high: 250 people would need to be treated for one year to prevent one death, non-fatal MI or non-fatal stroke. With Omacor priced at £13.89 per month, this raises serious concerns over cost-effectiveness. During the first 6 months of the study HDL, LDL and total cholesterol actually went up; at 42 months TC and LDL had fallen to baseline. On the basis of this trial, the SMC approved Omacor for use post MI in Scotland; NICE have recently taken the same decision in their *MI: secondary prevention* CG (May 2007) (see below). For patients with hypertriglyceridaemia, the effects of Omacor have been shown to be statistically significant in a number of small trials. No outcome data is available and there is no data to suggest advantage over existing therapy (e.g. fibrates).

NICE Recommendation:

NICE Clinical Guideline 48 *MI: secondary prevention* advises post MI patients to consume at least 7g of omega 3 fatty acids per week from two to four portions of oily fish. If patients have had an MI within 3 months and cannot consume oily fish on this scale, the prescriber is advised to *consider* providing at least 1g daily of omega-3-acid ethyl esters in a form licensed for secondary prevention post MI (the only licensed product is Omacor) for up to 4 years (the GISSI Prevenzione Study ran for 3.5 years). Omega-3-acid ethyl esters supplements should not routinely be prescribed for patients who have had an MI more than 3 months earlier.

PACEF Recommendation:

PACEF have reviewed the evidence base for Omacor and remain concerned over the application of the GISSI Prevenzione Study in a UK population and the poor cost-effectiveness of Omacor post MI. We entirely endorse the need for lifestyle change and support NICE advice that post MI patients should, if possible, consume two to four portions of oily fish per week. We have reviewed NICE CG 48 and acknowledge the role for multiple therapies post-MI, but have serious concerns around the risk of poor compliance with large multi-component prescriptions. With this in mind, we consider Omacor to be a low priority in these patients compared to other treatments. In addition, the lack of outcome data and comparative trials in hypertriglyceridaemia make us equally reluctant to endorse this indication. As a result of this, Omacor is classified as RED-RED. It should not be prescribed in either primary or secondary care in Lincolnshire even within the context endorsed by NICE. Prescribers are reminded that NICE CGs are advisory and implementation is not mandatory. Omega-3-acid ethyl ester supplements are stocked by many community pharmacies and health food shops, although the clinical efficacy and safety of these formulations has not been considered in randomized controlled trials in

a post MI population. Further discussion on other aspects of NICE CG 48 appears later in this bulletin.

TESTOSTERONE 2% GEL (TOSTRAN)

Testosterone 2% gel (Tostran) is a topical testosterone formulation licensed for testosterone replacement in male hypogonadism with confirmed testosterone deficiency. It is double the strength of existing formulations and marginally more expensive. The dose is 3g daily rather than 5g daily.

PACEF Recommendation:
Testosterone 2% gel (Tostran) is a reasonable alternative to other comparably priced topical testosterone formulations. It is classified as GREEN.

SODIUM VALPROATE MR CAPSULES (EPISENTA)

Sodium valproate (Episenta) MR capsules are competitively priced to other sodium valproate formulations. They are significantly cheaper than Epilim Chrono and standard release generic sodium valproate. Therapeutic switching is not recommended.

PACEF Recommendation:
Sodium valproate MR capsules (Episenta) are classified as GREEN.

TWO NEW COMBINED ORAL CONTRACEPTIVE AGENTS: KATYA AND SUNYA

Katya and Sunya are two new oral contraceptive agents containing different combinations of ethinyloestradiol and gestodene. The composition of Katya (30mcg ethinyloestradiol/75mcg gestodene per tablet) makes it directly comparable to Femodene and Minulet, while Sunya (20mcg ethinyloestradiol/75mcg gestodene per tablet) is equivalent to Femodette. Both Katya and Sunya are lower cost than equivalent preparations (see cost comparison below).

PACEF Recommendation:
Both Katya and Sunya tablets are classified as GREEN. The direct equivalence between Katya, Femodene and Minulet means that prescribers should select the agent of the lowest acquisition cost: Katya. Equally, Sunya should be prescribed in preference to the higher cost equivalent preparation, Femodette.

Product	Composition	Price
Katya tabs	**30mcg ethinyloestradiol/75mcg gestodene per tablet**	**3 x 21 £5.03**
Femodene tabs	30mcg ethinyloestradiol/75mcg gestodene per tablet	3 x 21 £7.18
Minulet tabs	30mcg ethinyloestradiol/75mcg gestodene per tablet	3 x 21 £6.36
Sunya tabs	**20mcg ethinyloestradiol/ 75mcg gestodene per tablet**	**3 x 21 £6.62**
Femodette tabs	20mcg ethinyloestradiol/ 75mcg gestodene per tablet	3 x 21 £9.45

NICE UPDATES

NICE TECHNOLOGY APPRAISAL 122: *ALTEPLASE FOR THE TREATMENT OF ACUTE ISCHAEMIC STROKE*

NICE have approved alteplase injection (Actilyse) for the treatment of acute ischaemic stroke when used by physicians trained and experienced in the management of acute stroke. It should be administered in centres with facilities that enable it to be used in full accordance with its marketing authorisation. The marketing authorisation specifies that treatment must be started within 3 hours of onset of stroke symptoms and after prior exclusion of intracranial haemorrhage by means of appropriate imaging techniques.

NICE CLINICAL GUIDELINE 48: *MI: SECONDARY PREVENTION*

In the following text, key NICE recommendations are summarized in bullet point format; PACEF recommendations reflecting practical detail follow in bold boxes.

General Lifestyle Recommendations

- Regular physical activity is advocated; this is defined as 20 to 30 minutes a day to the point of slight breathlessness.
- Smokers should be advised to quit and offered assistance to do so.
- Alcohol consumption should be kept within safe limits (21 units per week for men and 14 units per week for women). Binge drinking should be avoided.
- A Mediterranean-style diet is advocated involving more bread, fruit, vegetables and fish and replacing butter and cheese with products based on vegetable and plant oils.
- Patients are also advised to consume at least 7g of omega 3 fatty acids per week from two to four portions of oily fish. PACEF have decided not to endorse the NICE recommendation to consider providing at least 1g daily of omega-3-acid ethyl esters in a formulation licensed for secondary prevention post MI (i.e. Omacor) for up to 4 years for those who find oily fish unpalatable.

Drug Therapy

- All patients who have had an acute MI should be offered treatment with a combination of the following drugs: (1) ACE inhibitor, (2) aspirin, (3) beta-blocker, (4) statin.

ACE inhibitors

- Initiate ACEIs early after presentation and titrate up to the maximum tolerated or target dose. NICE suggest titration upwards at short intervals (e.g. every one to two weeks).
- Prior to initiating an ACEI (or an angiotensin receptor blocker) renal function, serum electrolytes and BP should be measured; after one to two weeks of starting treatment these parameters should be rechecked. Thereafter, at least annual checks are recommended with more frequent checks in those at risk of deterioration in renal function.
- ACEI treatment should be continued indefinitely in patients with preserved left ventricular function or with left ventricular systolic dysfunction (LVSD), whether or not they have heart failure symptoms.

- Angiotensin Receptor Blockers (ARBs) should be reserved for those intolerant to or allergic to an ACEI.
- Do not routinely use a combination of ACEI and an ARB for patients with heart failure and/or LVSD.

PACEF Recommendations:
Not all ACEIs are licensed for use following myocardial infarction. Currently licensed agents include captopril, lisinopril (short-term only), perindopril, ramipril and trandolapril. Ramipril remains the most cost-effective ACEI; it should be prescribed generically as capsules. The recommended dose after infarction is initially 2.5mg twice daily increased after 2 days to 5mg twice daily; standard maintenance therapy is 2.5 to 5mg twice daily. Expensive branded alternatives such as perindopril (Coversyl) and trandolapril (Gopten) are not recommended.

Antiplatelet therapy

- Aspirin should be offered to all patients after MI and continued indefinitely.
- Clopidogrel monotherapy should not be offered first line, but can be considered for patients with aspirin hypersensitivity.
- For patients with a history of dyspepsia consider a PPI and low-dose aspirin.
- For patients with a history of aspirin induced bleeding ulcers that have healed and who are *H. pylori* negative, consider a full-dose PPI and low dose aspirin.
- If the patient has not been treated with a combination of aspirin and clopidogrel during the acute phase of an MI, do not routinely initiate this combination.
- For non-ST-segment elevation acute coronary syndrome, use clopidogrel in combination with aspirin for 12 months after the most recent acute episode; use low dose aspirin alone thereafter.
- For ST-segment-elevation MI, continue aspirin and clopidogrel for at least 4 weeks; use low dose aspirin alone thereafter.
- For patients unable to take aspirin or clopidogrel consider moderate intensity warfarin (INR 2-3) for up to 4 years and possibly longer.
- For patients unable to tolerate clopidogrel and at low risk of bleeding consider aspirin and moderate intensity warfarin combined.
- The combination of warfarin and clopidogrel is not recommended.

PACEF Recommendations:
The recommended formulation and dose of aspirin is dispersible aspirin tablets 75mg once daily. Higher doses do not increase effectiveness, but can decrease tolerability. A patient must be truly hypersensitive to aspirin to warrant consideration of clopidogrel as a first line alternative. For patients experiencing dyspepsia with low dose aspirin, a low cost generic PPI should be considered (i.e. lansoprazole capsules 15 to 30mg or omeprazole capsules 10 to 20mg). Patients who have experienced aspirin induced bleeding ulcers should be considered for low-dose aspirin plus either concurrent lansoprazole 30mg daily or omeprazole 20mg daily. The clopidogrel component of aspirin-clopidogrel combination therapy should be discontinued after 4 weeks for ST segment elevation MI and 12 months for non-ST-segment elevation acute coronary syndrome.

Beta-blockers

- As soon as the patient is clinically stable, offer a beta-blocker (BB) and titrate upwards to the maximum tolerated dose. Continue indefinitely.
- For patients with LVSD, a BB licensed for use in heart failure may be preferred (e.g. carvedilol or bisoprolol).

Potassium channel activators

- Nicorandil (Ikorel) is not recommended to reduce cardiovascular risk.

Calcium channel blockers (CCBs)

- CCBs should not be used routinely for secondary prevention.
- If BBs are contra-indicated or need to be discontinued, consider diltiazem or verapamil for secondary prevention in patients without pulmonary congestion or LVSD.
- For patients who are stable, CCBs may be used to treat hypertension or angina. For patients with HF, use amlodipine.

Aldosterone antagonists

- For patients with signs and symptoms of heart failure and left ventricular systolic dysfunction post-MI, treatment with an aldosterone antagonist licensed for post-MI treatment (e.g.eplerenone (Inspra)) should be initiated within 3 to 14 days of the MI, preferably after the ACEI.
- Monitor renal function and serum potassium before and during treatment. If hyperkalaemia is a problem, halve the dose or stop treatment.

PACEF Recommendation:
PACEF will be reviewing the evidence base for eplerenone post-MI in comparison to spironolactone as part of our August work programme. At present, eplerenone is only recommended for use in county in patients intolerant to spironolactone.

Statins and other lipid lowering agents

- Following MI, statin therapy should be initiated with a statin of low acquisition cost.

PACEF Recommendation:
Generic simvastatin 40mg once daily each morning is advocated as the first line agent of choice. Current NHS policy advocates a total cholesterol target of 5mmol/l and an LDL-C target of 3mmol/l in secondary prevention. Approximately one third of patients may require upward dose titration or an alternative high-cost, high-potency statin to achieve the 5 and 3 target. Practices are urged not to pursue lower targets at this time.

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