NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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What's new this month:

- **PACEF have reconsidered the use of atorvastatin 80mg in patients with Acute Coronary Syndrome (ACS) and have approved it for use in patients at high risk subject to cardiologist initiation and review and step-down at six months (see page 2).**
- **The evidence around the use of enteric coated prednisolone is reviewed; prescribers are urged to use standard prednisolone tablets first line and to consider switching existing patients on EC to standard prednisolone (see page 3).**
- **Prednisone modified release tablets (Lodotra) are assessed and designated RED-RED (see page 4).**

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This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS Lincolnshire website (www.lpct.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: NOVEMBER 2010 UPDATE

Drug	Indication(s)	Traffic Light Status
Bendamustine (Levact)	Licensed for the treatment of indolent (low grade) non-Hodgkin's lymphoma that is refractory to rituximab or a rituximab containing regimen.	RED-RED
Eltrombopag tablets (Revolade)	Licensed for the treatment of chronic idiopathic thrombocytopenic purpura in splenectomised patients refractory to other treatments or as second line	RED-RED

	treatment in non-splenectomised patients when surgery is contra-indicated	
Ofatumumab intravenous infusion (Arzerra)	Licensed for the treatment of chronic lymphocytic leukaemia in patients refractory to fludarabine and alemtuzumab	RED-RED
Prednisone modified release tablets (Lodotra)	Licensed for the treatment of moderate to severe active rheumatoid arthritis (RA) in adults, particularly when accompanied by morning stiffness.	RED-RED

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care.**

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

REVIEW: ATORVASTATIN 80MG AND ACUTE CORONARY SYNDROME

ULHT Cardiologists have asked PACEF to review current guidance on the prescribing of statins for patients with Acute Coronary Syndrome (ACS). Existing PACEF guidance recommends that these patients should be treated as any other patient requiring secondary prevention of CVD and initiated on simvastatin 40mg with subsequent further titration to higher intensity statins only if necessary to achieve target. This decision was based on the absence of comparative data establishing definitively that ACS patients achieve better outcomes on high intensity statins than they do on simvastatin 40 or 80mg.

PACEF reviewed in more detail the cost model developed by NICE as part of Clinical Guideline 67, *Lipid Modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease* (May 2008). This cost model found that higher intensity statin therapy was cost-effective compared to low intensity statin therapy in patients following ACS. Treatment was most cost-effective using drugs with the lowest acquisition cost; this led to NICE advocating simvastatin 80mg as the first line high intensity statin of choice within this context. The cost model estimates that the lifetime incremental cost per Quality Adjusted Life Year (QALY) of using high intensity statins (atorvastatin 80mg/simvastatin 80mg) compared with low intensity statins (simvastatin 40mg /pravastatin 40mg) is about £4,700, indicating that high intensity statins are cost-effective in ACS patients. The NICE cost-effectiveness threshold is a cost per QALY of between £20,000 and £30,000. A similar figure derived from the same model for patients with coronary artery disease (CAD) calculates a cost per QALY figure of £27,840. This indicates that high intensity statins are not cost-effective in patients with stable CAD and justifies the prominent focus on low cost generic simvastatin 40mg first line in most patients requiring statin therapy within this context.

ULHT cardiologists estimate that they see approximately 800 new cases of ACS each year. All ACS patients now require a Global Registry of Acute Coronary Events (GRACE) score as part of their initial assessment after admission. The GRACE Risk Model is used to predict risk of in-hospital death. GRACE score points are determined from a range of features including: age, heart rate, systolic BP, creatinine level, cardiac arrest on admission, elevated cardiac markers and ST segment deviation. From this model, approximately 50% of ACS patients will emerge as very high risk. It was proposed to PACEF that this group of patients (approximately half) should be prioritised for initiation of atorvastatin 80mg once daily. All of this initiation would be by a cardiologist. As the highest risk period for these patients is the first 6 months after admission, it was also proposed that all high risk ACS patients should be reviewed after 6 months and stepped down to simvastastin 40mg where appropriate.

PACEF Recommendation:
NICE have confirmed that atorvastatin 80mg is cost-effective in the treatment of ACS. The compromise offered above enables the highest risk ACS patients to be treated with atorvastatin 80mg during their highest risk period with step-down to simvastatin 40mg after six months. The patent life of Lipitor is relatively short with the patent due to expire between November 2011 and May 2012. As a result of this, this advice will be reviewed within the next 12 months. All atorvastatin 80mg initiation within this context should be by a cardiologist; each patient initiated on atorvastatin 80mg for ACS will require a 6 month review and step down to simvastatin 40mg (unless above target, contra-indicated or the patient is taking potentially interacting medicines). Further onward titration may be necessary subject to response. Prescribers should remain aware of the poor cost-effectiveness of higher intensity statins, like atorvastatin and rosuvastatin, within the broader context of stable CAD.

REVIEW: STANDARD PREDNISOLONE TABLETS VERSUS ENTERIC COATED PREDNISOLONE TABLETS

Increasing scrutiny on improving prescribing cost-effectiveness, led PACEF to review the evidence for the use of enteric coated (EC) prednisolone tablets rather than the standard uncoated tablets. As far back as 1987, the *Drug and Therapeutics Bulletin* reviewed the topic and concluded that uncertainty remains as to whether enteric coating genuinely decreases the tendency of steroids to cause ulcers. Corticosteroid therapy itself has been weakly linked with an increased incidence of peptic ulcer (PU), particularly in patients with diseases linked to PU or with a history of PU; the risk also increases with steroid dose and duration. If a systemic ulcerogenic effect exists with corticosteroids, limiting local exposure with enteric coating is likely to make no difference to the risk while at the same time potentially compromising the bioavailability and efficacy of the steroid. Some commentators have suggested that dyspepsia is less common with EC, although this is opinion and has not been substantiated by evidence. In 1987, the overall conclusion of the *DTB* was that the use of EC prednisolone was speculative and probably generated a false sense of security in patients at high risk of or susceptible to PU.

Since the publication of this *DTB* over 20 years ago, there has been no further substantial review of this topic. Most recent published data has been limited to pharmacokinetic studies and case reports. Two recent small scale pharmacokinetic studies have confirmed findings from previously published work identifying a lower and slower time to peak plasma concentration with EC compared to uncoated

prednisolone, although bioavailability was generally found to be similar. The general conclusion from these studies was that absorption of corticosteroid from standard release prednisolone was more predictable than EC and less likely to result in therapeutic failure. A recent literature search undertaken by UK Medicines Information in January 2010 found five published case reports detailing therapeutic failure associated with EC prednisolone. These reports highlight significant inter-patient variability in absorption from EC prednisolone. Authors caution against the use of EC prednisolone in patients with Crohn's disease, any condition where there is a rapid GI transit time or diarrhoea, cystic fibrosis, ileostomy and any condition where prednisolone levels need to be stable and predictable.

In addition to this, there is a significant cost difference between EC and uncoated prednisolone tablets, with uncoated tablets costing considerably less:

Drug	**Strength**	**Cost per pack**
Prednisolone tablets	**1mg**	**£0.93 (28's)**
	5mg	**£1.03 (28's)**
Prednisolone EC tablets (generic)	2.5mg	£8.62 (28's)
	5mg	£8.69 (28's)
Prednisolone EC tablets (Deltacortril)	2.5mg	£1.16 (30's) £2.02 (100's)
	5mg	£1.19 (30's) £2.20 (100's)
Prednisolone soluble tablets	5mg	£8.95 (30's)
Prednisone modified release tablets (Lodotra)	5mg	£26.70 (30's) £89.00 (100's)
PPIs as prophylaxis against PU		
Omeprazole capsules	20mg daily*	£2.04 (28's)
Lansoprazole capsules	15-30mg daily*	15mg £1.78 (28's) 30mg £2.78 (28's)

*doses quoted as those used for prophylaxis against NSAID associated duodenal or gastric ulcer.

It has been estimated that annual savings in excess of £400,000 pa could be realised in Lincolnshire if all prednisolone EC 5mg were prescribed as standard prednisolone tablets. At present nearly 75% of all prednisolone prescribed in county is in the EC form. The Deltacortril brand of EC prednisolone is widely used as a way of minimising the cost of EC; severe availability problems with Deltacortril render this option temporarily impractical. Even prescribing standard prednisolone with concurrent gastro-protection, such as a low cost generic PPI, is cheaper, and probably more effective, than EC prednisolone prescribed alone.

PACEF Recommendation:

There is no strong evidence to support the use of EC prednisolone as a means to reduce the risk of PU associated with corticosteroid therapy. Corticosteroids appear to be weakly linked with PU with the risks dependent on dose and duration of treatment. Some commentators have suggested that dyspepsia is less common with EC, although this is opinion and has not been substantiated by evidence. A small number of published case studies have suggested that EC tablets are associated with less predictable absorption and more inter-patient variability than standard release formulations. This may be of clinical significance in those patients where plasma levels of prednisolone need to be stable and predictable or in those in whom GI transit time is compromised by disease or surgery. All PBC Clusters and practices are urged to consider switching patients currently taking EC prednisolone to standard prednisolone tablets. Support is available from the Prescribing and Medicines Management Team for practices wishing to do this. All new prednisolone prescribing should

be for the standard formulation. Where the patient has a history of PU or a disease linked to PU, concurrent gastroprotection with a low cost generic PPI is advised. When switching from EC to standard prednisolone tablets, monitor disease control.

RAPID DRUG ASSESSMENT: PREDNISONE MODIFIED RELEASE TABLETS (LODOTRA)

Lodotra is a new modified release (MR) tablet formulation of prednisone licensed for the treatment of moderate to severe active rheumatoid arthritis (RA) in adults, particularly when accompanied by morning stiffness. PACEF reviewed the evidence from one small (288 patients), short (12 weeks), randomised double-blind trial comparing Lodotra with standard prednisolone against a primary outcome measure of relative change in morning stiffness. The results show some benefit in the reduction of morning stiffness, although this is difficult to equate to actual clinical benefit such as increased mobility, reduction in need for rescue analgesia and improved quality of life. Ultimately, the small scale and short-term nature of the trial makes it difficult to draw firm conclusions around the potential role for prednisone MR in this long term, progressive and debilitating condition. In addition, prednisone MR (Lodotra) is considerably more expensive than existing standard release and enteric coated preparations of prednisolone as illustrated by the cost comparison table in the previous feature.

PACEF Recommendation:
There is no strong evidence to support the use of prednisone MR tablets (Lodotra) and they are prohibitively expensive in comparison to other formulations of prednisolone. As a result, they are designated RED-RED and should not be prescribed.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 202: *OFATUMUMAB FOR THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA REFRACTORY TO FLUDARABINE AND ALEMTUZUMAB* (OCTOBER 2010)

Key Recommendation

Ofatumumab is not recommended for the treatment of chronic lymphocytic leukaemia (CLL) that is refractory to fludarabine and alemtuzumab.

PACEF Recommendation:
Ofatumumab intravenous infusion (Arzerra) is designated RED-RED for the treatment of CLL refractory to fludarabine and alemtuzumab.

NICE TECHNOLOGY APPRAISAL 205: *ELTROMBOPAG FOR THE TREATMENT OF CHRONIC IMMUNE (IDIOPATHIC) THROMBOCYTOPENIC PURPURA* (OCTOBER 2010)

Key Recommendation

Eltrombopag is not recommended within its marketing authorisation for the treatment of chronic immune (idiopathic) thrombocytopenic purpura:

- in splenectomised adults whose condition is refractory to other treatments (for example, corticosteroids, immunoglobulins) or
- as second-line treatment in non-splenectomised adults where surgery is contraindicated.

PACEF Recommendation:
Eltrombopag tablets (Revolade) are designated RED-RED for this indication

NICE TECHNOLOGY APPRAISAL 206: *BENDAMUSTINE FOR THE TREATMENT OF INDOLENT (LOW GRADE) NON-HODGKIN'S LYMPHOMA THAT IS REFRACTORY TO RITUXIMAB* (TERMINATED APPRAISAL) (OCTOBER 2010)

Key Recommendation

NICE is unable to recommend the use of bendamustine for the treatment of indolent (low grade) non-Hodgkin's lymphoma that is refractory to rituximab or a rituximab containing regimen because no evidence submission was received from the manufacturer or sponsor of the technology.

PACEF Recommendation
Bendamustine (Levact) is not recommended for the treatment of indolent (low grade) non-Hodgkin's lymphoma that is refractory to rituximab or a rituximab containing regimen. Designation: RED-RED.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (SEPTEMBER 2010)

Isotretinoin: risk of serious skin reactions

- To date 66 cases of severe skin reactions have been reported worldwide with isotretinoin (Roaccutane). Examples include erythema multiforme (EM), Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
- Severe skin reactions of this nature can result in hospitalisation, disability, life-threatening events or death.
- If symptoms of EM, SJS or TEN develop, isotretinoin must be immediately discontinued.
- Patients starting isotretinoin should be informed of the signs and symptoms of these skin diseases and advised to stop treatment and seek medical advice immediately if symptoms arise.

Inhaled and intranasal corticosteroids: risk of psychological and behavioural side effects

- Inhaled and intranasal corticosteroids have been associated with a range of psychological or behavioural effects including: psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression (particularly in children).

Long-acting beta 2 agonists: reminder for use in children and adults in asthma

- In asthma, always prescribe a LABA with concomitant inhaled corticosteroid (ICS), but only when an ICS alone is not sufficient to control asthma symptoms.
- LABA should not be initiated in patients with rapidly deteriorating asthma.

- Review LABA therapy regularly, prescribe the lowest effective dose and stop if there is no benefit.
- Stepping down therapy should be considered when good long-term asthma control has been achieved.
- LABA should not be prescribed for the relief of exercise induced asthma in the absence of regular ICS.
- A daily dose of 24 micrograms of formoterol is sufficient for most children, particularly for younger age groups. Higher doses should be used rarely.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (OCTOBER 2010)

Implanon contraceptive implant: changing to Nexplanon

- In October 2010, Nexplanon replaces the Implanon contraceptive implant.
- All healthcare professionals trained to insert Implanon need to ensure that they are fully trained to use Nexplanon.

Codeine-containing liquid over-the-counter medicines: should not be used for cough under 18 years

- The Commission on Human Medicines have advised that codeine containing OTC liquid medicines should not be used for cough suppression in children and young people younger than 18 years.
- New packaging and leaflets for OTC liquid cough preparations containing codeine will not be available until April 2011.
- Pharmacists are asked to consider this new advice when recommending OTC cough preparations for children.

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