Lincolnshire NHS

Prescribing and Clinical Effectiveness Bulletin

Volume 1; Number 5 **October 2007**

CONTENTS

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/OCTOBER UPDATE

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

Drug	Indication	Traffic Light Status
Adalimumab (Humira)	**Licensed for the treatment of active and progressive psoriatic arthritis that has not responded adequately to other disease modifying anti-rheumatic drugs (DMARDs).**	**RED**
Beclometasone 5mg sustained release tablet (Clipper)	**Licensed for use in combination with aminosalicylates for mild to moderate ulcerative colitis in patients unresponsive to**	**RED-RED pending specialist review**

	aminosalicylates.	
Emollin Emollient Spray	**A spray emollient licensed for topical application to dry, scaly, sensitive or sore skin.**	**GREEN**
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)
Exenatide (Byetta)	**Treatment of type 2 diabetes in combination with metformin and sulphonylureas**	**RED-RED (N.B. This decision will be reviewed in early 2008 following the publication of the updated NICE Clinical Guideline on the management of type 2 diabetes)**
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)
Lidocaine Medicated Plaster 5% (Versatis)	**A local anaesthetic plaster licensed for the treatment of postherpetic neuralgia**	**AMBER for post-herpetic neuralgia subject to specialist initiation after all other alternatives have been tried. Designated as RED-RED for neuropathic pain (unlicensed).**
Natalizumab inf (Tysabri)	**Highly active relapsing remitting multiple sclerosis**	**RED**
Pemetrexed (Alimta)	**Treatment of locally advanced or metastatic non-small cell lung cancer**	**RED-RED (Not recommended by NICE)**
Ranibizumab (Lucentis)	Treatment of neovascular (wet) age-related macular degeneration (AMD).	RED-RED
Rituximab (MabThera)	**Licensed in combination with methotrexate for the treatment of severe active rheumatoid arthritis in patients who have not responded adequately to other DMARDs or who are intolerant of them.**	**RED**
Sensicare Emollient	**A petroleum and glycerin based emollient licensed for dry skin conditions**	**GREEN**
Sitagliptin (Januvia)	**A member of a new class of oral hypoglycaemic drugs indicated for use with metformin or a glitazone in type 2 DM inadequately controlled by diet , exercise and either metformin or a glitazone.**	**RED-RED (N.B. This decision will be reviewed in early 2008 following the publication of the updated NICE Clinical Guideline on the management of type 2 diabetes and the launch of vildagliptin)**
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.

NEW LINCOLNSHIRE TRAFFIC LIGHT LIST

The Lincolnshire Traffic Light List has now been fully revised and updated. The List summarizes the Lincolnshire Healthcare Community view on a wide range of different specialist medicines utilizing the colour coded shorthand detailed in the box above. It is intended to act as a resource document for all clinicians working within Lincolnshire NHS including doctors, pharmacists and nurses working in acute services and mental health, GPs and their staff, non-medical prescribers, community nurses and retail pharmacists.

As the majority of products prescribed in primary care will be classified as GREEN, it is deemed to be impractical to include a green list. As a result of this, only products classified as RED-RED (DOUBLE RED), RED or AMBER will be included. The PACEF New Drug Assessment Group will endeavour to produce assessments on all significant new products as soon as possible after launch. At present we are managing to do this within the first three months of the life of each product. As all new products are designated as RED-RED pending assessment, prescribers are asked to wait for guidance from PACEF before initiating treatment with a new product or accepting a request from a specialist to prescribe. Omission of a drug from the Traffic Light List cannot be taken to indicate that it is recommended for prescribing in either primary or secondary care; if you are unsure of the status of a particular established medicine please contact your local prescribing adviser for guidance.

There have been some changes to the format of the List following comments received from prescribers. These include:

- Drugs are now listed by approved name in alphabetical order.
- The listed clinical indication is the one covered by the Traffic Light classification. In some cases products will have more than one entry if there are different classifications for different indications.
- The comments section provides a brief explanation of the rationale behind the classification decision.
- If national guidance is available, brief details are given in the far right hand column.

The Traffic Light List will be updated following each PACEF meeting and copies will be available on the PCT intranet site, ULH intranet site and from members of the PCT Prescribing & Medicines Management Team. Updated information will also be circulated monthly in the *PACE Bulletin.*

SAFETY CONCERNS ASSOCIATED WITH ROSIGLITAZONE

In response to mounting concerns relating to the safety of glitazones, in particular rosiglitazone, PACEF have reviewed the evidence base to date. A number of key studies have contributed significantly to heightened levels of concern. In May 2007, a meta-analysis of data from 42 trials involving 27,800 patients showed a significantly greater number of myocardial infarction events associated with rosiglitazone, but a non-significant increase in the number of deaths from cardiovascular causes. The authors concluded that rosiglitazone may be associated with an increased risk of myocardial infarction and possibly cardiovascular death[1]. At present, these concerns are confined to rosiglitazone as evidence from the PROactive study showed no significant difference in cardiovascular events in pioglitazone treated patients compared to placebo.

Following on from this meta-analysis, an unscheduled interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study was carried out [2]. This study is a six year long-term open label RCT comparing metformin or a sulphonylurea with or without rosiglitazone in patients with type 2 diabetes. The interim analysis undertaken after 3.75 years showed no significant differences in the primary endpoints of hospitalisation or death from CV causes, although it is not clear if a statistical difference will emerge on completion of the trial. Additionally, results showed a doubling of the risk of heart failure with rosiglitazone.

A subsequent Cochrane Collaboration review published in July emphasized the lack of trial evidence relating rosiglitazone to improvements in patient orientated outcomes such as mortality, morbidity, adverse effects or health related quality of life[3]. The review also highlighted the increased risk of oedema with rosiglitazone and a number of reports that link both pioglitazone and rosiglitazone to adverse changes in bone with increased incidence of fractures.

Finally, a study on the link between glitazones and heart failure was widely reported in the news at the end of July and published in the journal *Diabetes Care* [4]. This was the results of a teleo-analysis of RCTs, observational studies, anecdotal reports, case series and spontaneous reports in the Canadian Drug Monitoring program. This analysis concluded that the risk of heart failure was increased for patients prescribed glitazones with an estimate of the number needed to harm to be over 20 over a 2.2 year period.

Both the European Medicines Agency (EMEA) and the MHRA have issued advice reminding prescribers to adhere to the prescribing restrictions outlined in product information; patients are advised not to stop treatment but to discuss any concerns relating to their medication with their GP at their next appointment [5,6].

PACEF Recommendations:
Prescribers are reminded that glitazones are advocated by NICE as third line agents in the treatment of type 2 diabetes and that this is likely to be reinforced in the updated NICE clinical guideline due for publication in the new year. They should only be utilized in patients unable to tolerate metformin and

sulphonylurea combination therapy or in those for whom either metformin or a sulphonylurea are contra-indicated or inappropriate. Where a glitazone is indicated, pioglitazone should be considered first due to its lower acquisition cost and fewer concerns over cardiovascular safety. Patients who are currently well controlled and stable on rosiglitazone should be enabled to continue. Both pioglitazone and rosiglitazone are contra-indicated in patients with cardiac failure or a history of cardiac failure. Fluid retention is well documented with glitazones and may exacerbate or precipitate heart failure, particularly in patients at risk (e.g. those with a prior MI or symptomatic coronary artery disease, the elderly, those with mild to moderate renal failure, those on concurrent NSAID or insulin therapy). Patients deemed to be at risk should be observed for signs and symptoms of heart failure, weight gain and fluid retention. The increased fracture risk with both of the glitazones necessitates the need for caution in those at risk.

References

1. Nissen SE & Wolski K. *N Engl J Med* 2007; 356:2457-71
2. Home PD et al. *N Engl J Med* 2007; 357:28-38
3. Richter et al Cochrane Database of Systemic Reviews 2007, issue 3 EMEA Press Release – Statement on recent publication on cardiac safety of rosiglitazone. 23 May 2007
4. Singh S, Loke YK et al. J. *Diabetes Care* 2007:30:2148-2153
5. EMEA Press Release – Statement on recent publication on cardiac safety of rosiglitazone. 23 May 2007
6. MHRA statement on cardiac safety of rosiglitazone. 23 May 2007

NEW DRUG ASSESSMENTS

EXENATIDE (BYETTA)

Exenatide (Byetta) is a new twice daily sub-cutaneous injection licensed for the treatment of Type 2 diabetes in combination with metformin and sulphonylureas where adequate glycaemic control has not been achieved.on maximally tolerated doses of these agents alone. It is an incretin mimetic that acts by stimulating secretion of insulin from pancreatic beta cells; use is dependent upon the patient still having residual beta cell activity. Exenatide also suppresses the secretion of glucagons and slows gastric emptying thus reducing the rate at which meal-derived glucose appears in the circulation. It also decreases appetite and increases satiety.

Trial data available to date includes three 30 week triple blind placebo controlled trials (involving 1,446 patients) assessing the addition of exenatide 5mcg or 10mcg to maximally effective doses of metformin (≥1500mg), a sulphonylurea or a combination of both in adults. In all three studies, the addition of exenatide was associated with significant advantages over placebo for the primary endpoint of change in baseline HbA_{1c} and for the secondary endpoints of reductions in fasting glucose concentrations and body weight; the proportion of patients attaining an HbA_{1c} of ≤7% was also increased. In addition, two randomised open label studies have compared fixed doses of exenatide 10mcg twice daily to insulin glargine once daily over 26 weeks and insulin aspart twice daily over 52 weeks in patients inadequately controlled using a combination of metformin and a sulphonylurea. A further study compared exenatide and insulin glargine over treatment periods of 16 weeks in patients failing to achieve control with metformin or sulphonylurea monotherapy. In these studies it was noted that body weight decreased in the exenatide groups and increased in all three insulin groups. Exenatide given up to one year was associated with weight loss in the range of 0.9 to 2.8kg compared to that of 0.3 to 0.9kg with placebo and a weight gain of 0.35 to 2.9kg with insulin. At present, there are no trials comparing exenatide with a glitazone despite the fact that the glitazones are the most prominent third line alternative therapies. There is also no outcome data

demonstrating the effectiveness or otherwise of exenatide in the prevention of macrovascular or microvascular complications.

The most frequently reported adverse effects with exenatide are hypoglycaemia (26.6% of patients and mainly associated with concurrent sulphonylurea use), nausea and vomiting. Mild to moderate nausea occurred in 33 to 57% of patients in comparative studies; it appears to be more common in the first weeks of treatment**.** The product is specifically contra-indicated in type 1 diabetes and in type 2 diabetic patients on insulin.

Exenatide is a premium price preparation expensive even by the standards of higher doses of established glitazones:

Exenatide 5 mcg and 10mcg 60 dose prefilled pen	**£68.24**
Pioglitazone 15mg tablets (28 tabs)	£24.14
Pioglitazone 30mg tablets (28 tabs)	£33.54
Rosiglitazone 4mg tablets (28 tabs)	£24.74
Rosiglitazone 8mg tablets (28 tabs)	£50.78

PACEF Recommendation:
PACEF were concerned about the lack of outcome data with exenatide as well as the lack of comparative data against glitazones. The poor tolerability in terms of gastrointestinal side effects and the lack of cost-effectiveness data, particularly in light of the high comparative cost against alternative therapies, also raised concerns. As a result of this, exenatide is designated RED-RED. This decision will be reviewed early in the new year following publication of the NICE Clinical Guideline on the management of type 2 diabetes.

SITAGLIPTIN (JANUVIA)

Sitagliptin is from a new class of oral antidiabetic agents known as the dipeptidyl peptidase type 4 (DPP- 4) inhibitors. It works by enhancing the levels of active incretin hormones which increase insulin secretion, reduce the secretions of glucagons and thereby reduce blood glucose levels. It is licensed for the treatment of type 2 diabetes in combination with metformin when diet and exercise plus metformin do not provide adequate glycaemic control. It is also indicated in combination with a glitazone when diet and exercise plus a glitazone do not provide adequate glycaemic control.

Key studies to date include a randomized controlled trail (RCT) of 701 patients with type 2 diabetes and inadequate glycaemic control despite treatment with metformin (≥1500mg /day). Patients were randomized to either metformin plus placebo or metformin plus sitagliptin 100mg once daily for 24 weeks. In a second RCT, 353 type 2 diabetic patients were randomised to pioglitazone monotherapy plus placebo or pioglitazone plus sitagliptin 100mg once daily for 24 weeks. Both of these studies showed statistically significant improvements in glycaemic endpoints compared to placebo. A further RCT of 1,172 patients lasting 52 weeks assessed the efficacy of adding either sitagliptin 100mg daily or dose tritrated glipizide to ongoing metformin therapy. The results showed that sitagliptin was non- inferior to glipizide in HbA_{1c} reduction at 52 weeks. In summary, when used second line in the treatment of type 2 diabetes sitagliptin is effective at improving glycaemic control and reducing HbA_{1c} levels and is not inferior to existing sulphonylureas. There is no comparative data against glitazones within a second or third line context involving combination therapy

with metformin; nor is there any long-term safety data beyond 52 weeks nor evidence of improvement in macrovascular or microvascular outcomes.

Data from published trials, abstracts and poster presentations all suggest that sitagliptin is well tolerated. The incidence of hypoglycaemia is comparable to placebo; this offers one potential advantage over existing sulphonylureas. Sitagliptin is weight neutral; approximately 5% of patients report osteoarthritis or pain in the extremities.

Sitagliptin is a premium priced preparation significantly more expensive than existing sulphonylureas:

Sitagliptin 100mg daily	**£33.36**
Gliclazide 80mg (twice daily)	£2.19
Glipizide 5mg (max dose 20mg daily)	£11.44

PACEF Recommendation:
PACEF remain unconvinced of the benefits of sitagliptin beyond existing therapies. The lack of long-term safety data and any clinically relevant outcomes data plus the high cost in comparison to well established sulphonylureas all give cause for concern. As a result of this, sitagliptin has been designated RED-RED. The imminent launch of vildagliptin (Galvus) plus the forthcoming update of the NICE Clinical Guideline on the management of type 2 diabetes will necessitate a further review of gliptins in the coming months.

LIDOCAINE MEDICATED PLASTER 5% (VERSATIS)

Versatis is a lidocaine containing medicated plaster that produces a local analgesic effect at the site of application. It is licensed for the treatment of neuropathic pain associated with previous herpes zoster infection (post-herpetic neuralgia (PHN)). The evidence base for the product amounts to five small-scale studies of variable quality of which only two have been published in full. Although trial results show statistically significant improvements in pain relief and pain intensity scores, it is difficult to translate these into actual clinical benefit. There are no comparative studies with existing systemic or topical therapies and no specific data is available on the use of the patch as adjunct therapy. Despite the poor evidence base, PHN is acknowledged as a potentially debilitating condition which can have a significant impact on an individual's quality of life and the trials provide some evidence that lidocaine plasters may provide some relief. However, comparative costs versus alternative therapies are prohibitive:

Drug	Daily dose range	Cost for 28 days
Lidocaine 5% patch	**1 - 3 patches**	**£68 - £203**
Capsaicin 0.075% cream*	Apply 3-4 times daily	£12.15
Gabapentin	900-1800mg	£10.15 - £89.04
Pregabalin	150-600mg	£96.60
Carbamazepine	400-1600mg	£6.04 – £11.80
Carbamazepine s/r	400-1600mg	£5.26 - £20.68
Amitriptyline	25-75mg	£1.48 - £4.44

*based on 1x 45g lasting 28 days

PACEF Recommendation:
Lidocaine Medicated Plaster (Versatis) has been designated as AMBER for post-herpetic neuralgia; this is subject to specialist initiation after all other alternatives have been tried. The product remains RED-RED for other types of neuropathic pain. In view of the limited evidence of efficacy, lack of comparative data with alternative treatments and higher drug costs, use is expected to be in individuals in whom existing treatments have failed or are not tolerated or where compliance issues with oral medication preclude oral treatment. Prescribers are reminded that the high cost of the product should preclude consideration except as a last resort.

RAPID ASSESSMENTS

EMOLLIN EMOLLIENT SPRAY

PACEF Recommendation:
Emollin is the only spray emollient currently available and is comparably priced with alternative branded emollients. PACEF designation: GREEN.

SENSICARE EMOLLIENT

PACEF Recommendation:
Sensicare is a new petroleum and glycerin based emollient comparably priced with generic and branded alternatives. PACEF designation: GREEN.

BECLOMETASONE 5MG TABLETS (CLIPPER)

PACEF Recommendation:
Clipper is a beclometasone 5mg sustained release tablet licensed in combination with aminosalicylates for mild to moderate ulcerative colitis unresponsive to aminosalicylates alone. The product is designated as RED-RED pending specialist review.

NICE TECHNOLOGY APPRAISAL 124: PEMETREXED FOR THE TREATMENT OF NON-SMALL-CELL LUNG CANCER

Key points from the TA are as follows:

- Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small-cell lung cancer.
- Patients currently receiving the drug should have the option to continue therapy until they or their clinicians consider it appropriate to stop.

PACEF Recommendation:
Pemetrexed (Alimta) is designated as RED-RED and is not recommended for the treatment of locally advanced or metastatic non-small-cell lung cancer.

NICE TECHNOLOGY APPRAISAL 125: ADALIMUMAB FOR THE TREATMENT OF PSORIATIC ARTHRITIS

Key points from the TA are as follows:

- Adalimumab, within its licensed indication, is recommended as an option for the treatment of adults with active and progressive psoriatic arthritis. The drug is licensed for the treatment of active and progressive psoriatic arthritis that

has not responded adequately to other disease modifying anti-rheumatic drugs (DMARDs).

- The person must have peripheral arthritis with three or more tender joints or three or more swollen joints.
- The psoriatic arthritis must have not responded to adequate trials of at least two standard DMARDs, administered individually or in combination.
- Adalimumab should be discontinued after 12 weeks if there is not an adequate response assessed using the psoriatic arthritis response criteria (PsARC).
- Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of psoriatic arthritis.

PACEF Recommendation:
Adalimumab (Humira) is designated as RED and should only be prescribed within NICE criteria by specialist physicians in secondary or tertiary care.

NICE TECHNOLOGY APPRAISAL 126: RITUXIMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

Key points from the TA are as follows:

- Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis (RA) who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs) including treatment with at least one tumour necrosis factor alfa inhibitor therapy (i.e. adalimumab, etanercept or infliximab).
- Treatment should be continued only if there is an adequate response following initiation of therapy. An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more. Repeat courses should be given no more frequently than every 6 months.
- Treatment should be initiated, supervised and treatment response assessed by specialist physicians experienced in the diagnosis and treatment of RA.

PACEF Recommendation:
Rituximab (MabThera) is designated as RED for the treatment of severe RA within the criteria designated by NICE. The drug is administered as an IV infusion and will only be used under specialist supervision within secondary care or tertiary care.

NICE TECHNOLOGY APPRAISAL 127: NATALIZUMAB FOR THE TREATMENT OF ADULTS WITH HIGHLY ACTIVE RELAPSING-REMITTING MULTIPLE SCLEROSIS

Key points from the TA are as follows:

- Natalizumab is recommended as an option for the treatment of rapidly evolving severe relapsing-remitting multiple sclerosis (RES).
- RES is defined as two or more disabling relapses in one year and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.
- People currently receiving natalizumab outside the criteria outlined in the TA should have the option to continue therapy until they or their clinicians consider it appropriate to stop.

PACEF Recommendation:
Natalizumab (Tysabri) should be reclassified from RED-RED to RED.

Stephen Gibson
Head of Prescribing and Medicines Management
Lincolnshire PCT
steve.gibson@lpct.nhs.uk

Cathy Johnson
Interface Lead Pharmacist
Lincolnshire PCT
cathy.johnson@lpct.nhs.uk

16th October 2007