NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 20 **November 2010**

What's new this month:

- **The PACEF position on agomelatine (Valdoxan), a new antidepressant, has been reviewed. Agomelatine (Valdoxan) remains RED. All prescribing should be handled by specialists in mental health; GPs are not expected to prescribe (see page 2).**
- **Rupatadine (Rupafin), a new non-sedating antihistamine, has been assessed and designated RED-RED. Low cost generic non-sedating antihistamines are preferred (e.g. cetirizine 10mg tablets or loratidine 10mg tablets) (see page 3).**
- **Sevelamer carbonate powder (Renvela) has been designated AMBER for the control of hyperphosphataemia in adult patients on haemodialysis or with chronic kidney disease. The shared care guideline covering sevelamer hydrochloride tablets (Renagel) has been expanded to cover both formulations and is now available (see page 4).**
- **Ivabradine (Procoralan) in heart failure and bisphosphonates and cancer risk are reviewed in our New Trials in Brief section (see pages 5 to 7).**
- **Updated *Guidelines for the treatment of commonly occurring infections in Lincolnshire primary care* have been issued for Winter 2010/11 (see page 7)**

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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: SEPTEMBER 2010 UPDATE

Drug	Indication(s)	Traffic Light Status
Adalimumab injection (Humira)	Licensed for psoriatic arthritis	RED
Agomelatine 25mg tablets (Valdoxan)	Licensed for the treatment of major depressive episodes in adults.	RED
Etanercept injection (Enbrel)	Licensed for psoriatic arthritis	RED
Infliximab intravenous infusion (Remicade)	Licensed for psoriatic arthritis	RED
Rupatadine 10mg tablets (Rupafin)	Licensed for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria (CIU) in adults and adolescents	RED-RED
Sevelamer carbonate 2.4g powder (Renvela)	Licensed for the control of hyperphosphataemia in adult	AMBER Revised shared care guideline for

	patients (1) receiving haemodialysis or peritoneal dialysis or (2) with Chronic Kidney Disease (CKD) not on dialysis with a serum phosphate greater than or equal to 1.78 mmol/l.	sevelamer formulations is now available
Tocilizumab infusion (RoActemra)	Licensed for use in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis	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 within**

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: AGOMELATINE 25MG TABLETS (VALDOXAN)

In September 2009, PACEF undertook a New Drug Assessment on agomelatine 25mg tablets (Valdoxan) (see *PACE Bulletin* Vol 3, No 11 (October 2009). Agomelatine is a novel antidepressant agent that acts at both melatonergic and 5-HT_{2C} receptors; the mechanism by which this alleviates depression remains unclear at present. The product is licensed for the treatment of major depressive episodes in adults.

PACEF reviewed data from short-term, small-scale clinical trials that established agomelatine as at least equal in efficacy to sertraline, fluoxetine and venlafaxine (although the clinical significance of this remains unclear). Promisingly, early trial data also revealed a lower rate of adverse effects with agomelatine in comparison to alternatives. However, PACEF were concerned about the lack of long term safety and efficacy data and the high cost of agomelatine in comparison to most alternatives (see Cost Comparison below):

Treatment	**30 day treatment cost Minimum**	**30 day treatment cost Maximum**
Fluoxetine 20mg daily		£1.90
Citalopram 20mg daily		£1.39
Lithium 800mg daily		£2.10
Sertraline 50-200mg daily	£1.23	£3.28
Paroxetine 20-50mg	£2.29	£5.46
Moclobemide 300-600mg daily	£5.91	£11.82
Mirtazapine 30-45mg daily	£2.19	£3.98
Escitalopram 10-20mg daily	£15.98	£27.00
Duloxetine 60mg daily		£29.70
Agomelatine 25mg-50mg daily	**£41.28**	**£82.56**
Venlafaxine XL (Efexor XL) 150-225mg daily	£40.19	£64.30

Venlafaxine XL 150-225mg + Mirtazapine 30mg daily	£42.38	£66.49

As a result of this, agomelatine 25mg tablets (Valdoxan) were designated RED, for use within Lincolnshire Partnership Foundation Trust only.

At the October 2010 meeting of PACEF, all of the original trials plus any new trials involving agomelatine that had been published since the original assessment were reviewed. Original trial data establishes agomelatine as at least equally effective to sertraline, fluoxetine and venlafaxine with a side-effect profile comparable to placebo. Common side-effects reported were headache, dizziness, somnolence, insomnia, migraine, nausea, diarrhoea, constipation and >3 times upper normal range ALT and/or AST. With agomelatine Liver Function Tests (LFTs) are recommended at initiation, 6 weeks, 12 weeks, 24 weeks and thereafter when clinically indicated. Agomelatine seems to have a neutral effect on body weight, heart rate and blood pressure and abrupt withdrawal has not been associated with discontinuation symptoms.

PACEF retain some reservations about the original comparative trials as the comparator drug is sometimes compromised by the use of sub-optimal doses or inadequate dose titration. Many of these trials are also more concerned with primary endpoints such as 'getting to sleep' score, changes in sexual function and improvement in rest/activity circadian rhythms than improvement in depression that often features as a secondary endpoint

PACEF Recommendation

PACEF has updated its review of agomelatine (Valdoxan), but can find no compelling reason to change the original decision of September 2009, particularly in light of the high comparative cost of the product. As a result of this, agomelatine continues to be designated RED. It can be prescribed solely by specialists within Lincolnshire Partnership Foundation Trust. Agomelatine is not approved for use within primary care; any requests to GPs from specialists to prescribe should be refused. This decision is subject to review pending the emergence of further evidence.

RAPID DRUG ASSESSMENT: RUPATADINE 10MG TABLETS (RUPAFIN)

Rupatadine (Rupafin) is a second generation (non-sedating) antihistamine licensed for the symptomatic treatment of allergic rhinitis and chronic idiopathic urticaria (CIU) in adults and adolescents (over 12 years of age). Early pharmacological studies have shown that it is a dual inhibitor of both histamine H1 and platelet activating factor (PAF) receptors and therefore inhibits a range of mediators involved in both the early and late phases of the inflammatory process. Most antihistamines do not have an inhibitory effect on PAF receptors, although the clinical significance of this remains unclear.

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Evidence supportive of rupatadine's role in the management of CIU comes from two small trials and a pooled analysis from a further two trials. Results demonstrate that it has a rapid onset of action (within 12 hours of the first dose), helps to reduce pruritis (the most troubling symptom of CIU) and reduces the number of wheals compared to placebo. There is a lack of comparative data against other oral non-sedating antihistamines used for the management of CIU.

A cost comparison reveals the following:

Drug	Daily dose range	Cost (£) 30tabs
Rupatadine 10mg tablets (Rupafin)	10mg daily	£5.00
Cetirizine 10mg tablets	**10mg daily**	**£0.95**
Desloratadine 5mg tablets (Neoclarityn)	5mg daily	£6.77
Fexofenadine 180mg tablets	180mg daily	£3.68
Levoceterizine 5mg tablets	5mg daily	£4.39
Loratadine 10mg tablets	**10mg daily**	**£1.20**
Mizolastine 10mg MR tablets (Mizollen)	10mg daily	£5.77

(Prices compiled from *Drug Tariff* November 2010)

PACEF Recommendation

PACEF remain concerned over the small scale and short duration of the published trials associated with rupatadine. CIU is a long term condition and long term safety and efficacy data in comparison to alternative agents is required. Where a once daily non-sedating antihistamine is required, generic cetirizine 10mg tablets or loratidine 10mg tablets are preferred first line. Rupatadine 10mg tablets (Rupafin) are designated RED-RED.

RAPID DRUG ASSESSMENT: SEVELAMER CARBONATE POWDER (RENVELA)

Sevelamer carbonate powder (Renvela) is a phosphate binder licensed for the control of hyperphosphataemia in adult patients:

- receiving haemodialysis or peritoneal dialysis
- with Chronic Kidney Disease (CKD) not on dialysis with a serum phosphate greater than or equal to 1.78 mmol/l.

Sevelamer hydrochoride tablets (Renagel) were reviewed by PACEF in 2007 and were designated AMBER (see *PACE Bulletin*, Vol1 No 6). The powder formulation is similarly priced to the tablets and is designed for patients unable to swallow Renagel tablets.

In one study in 79 haemodialysis patients, it was found that sevelamer carbonate and sevelamer hydrochloride were equivalent in controlling serum phosphate; serum bicarbonate levels increased with sevelamer carbonate. Fewer gastrointestinal side effects were reported in the sevelamer carbonate group. Subsequent studies have shown similar findings.

PACEF Recommendation:

Sevelamer carbonate powder (Renvela) is designated AMBER. Existing shared care guidelines for sevelamer hydrochloride tablets (Renagel) have been expanded to include sevelamer carbonate powder (Renvela). Sevelamer should only be initiated by a specialist within the context of the SCG. Sevelamer carbonate powder (Renvela) should be used for those patients unable to swallow Renagel tablets.

NICE TECHNOLOGY APPRAISAL 198: *TOCILIZUMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS* (AUGUST 2010)

Key recommendations

Tocilizumab, in combination with methotrexate (MTX), is recommended for the treatment of moderate to severe active rheumatoid arthritis in people whose rheumatoid arthritis has responded inadequately to one or more tumour necrosis factor alpha (TNF-a) inhibitors and (1) whose rheumatoid arthritis has responded inadequately to rituximab or (2**)** in whom rituximab is contraindicated or when rituximab is withdrawn because of an adverse effect.

PACEF Recommendation:
Tocilizumab infusion (RoActemra) is designated RED for the treatment of moderate to severe active rheumatoid arthritis in combination with MTX.

NICE TECHNOLOGY APPRAISAL 199: *ETANERCEPT, INFLIXIMAB AND ADALIMUMAB FOR THE TREATMENT OF PSORIATIC ARTHRITIS* (AUGUST 2010)

Key recommendations

Etanercept, infliximab and adalimumab are recommended for the treatment of adults with active and progressive psoriatic arthritis when the following criteria are met

- The person has peripheral arthritis with three or more tender joints and three or more swollen joints, and
- The psoriatic arthritis has not responded to adequate trials of at least two standard disease-modifying antirheumatic drugs (DMARDs), administered either individually or in combination.

Etanercept, adalimumab or infliximab treatment should be discontinued in people whose psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 12 weeks. An adequate response is defined as an improvement in at least two of the four PsARC criteria, (one of which has to be joint tenderness or swelling score) with no worsening in any of the four criteria. People whose disease has a Psoriasis Area and Severity Index (PASI) 75 response at 12 weeks but whose PsARC response does not justify continuation of treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response.

PACEF Recommendation
Etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira) are all designated RED for the psoriatic arthritis indication.

NEW TRIALS IN BRIEF

Antipsychotics in early psychosis

This meta-analysis of 15 randomised controlled trials (RCTs) (n=2522) compared first generation antipsychotics (FGAs or typical antipsychotics) with second generation antipsychotics (SGAs or atypical antipsychotics) in the treatment of early phase psychosis. No statistically significant difference was found between the two groups with regard to their effects on symptoms and discontinuation rates at 12

months. Patients taking SGAs gained an average of 2.1 kg more weight than those on FGAs, whereas those on FGAs experienced more extrapyramidal side effects.

PACEF comment:
Over a number of years, SGAs (or atypical antipsychotics) have been increasingly used in the treatment of psychosis in preference to FGAs. Previous NICE guidance tended to support the preferential use of SGAs because of a perceived beneficial side effect profile. Current NICE guidance on schizophrenia (2009) does not give preference to SGAs over FGAs because awareness of the different, but equally undesirable, side effects of SGAs has increased. This meta-analysis supports this position demonstrating that there is no clear evidence of advantages in terms of symptom control or likelihood of discontinuation. The differing propensity of individual drugs to cause particular side effects is more important in guiding choice for individuals.

Reference
Crossley N et al. Efficacy of atypical vs. typical antipsychotics in the treatment of early psychosis: meta-analysis. *Br J Psych* 2010; 196: 434-439.

The SHIFT Study: Ivabradine in heart failure

Stable heart failure patients (n=6558) who had at least one hospital admission for heart failure in the last year were randomised to ivabradine or placebo with a median follow up of 22.9 months. The composite primary endpoint of cardiovascular (CV) death or hospital admission for worsening heart failure was reduced in the ivabradine group compared to placebo (24% vs 29%). The effects were driven mainly by a reduction in hospital admissions for heart failure and deaths due to heart failure. There were no statistically significant differences in the secondary endpoints of all cause mortality or CV mortality.

PACEF comment:
This study was publicised in the general media and demonstrates some beneficial effects of ivabradine in the treatment of heart failure. Ivabradine reduced cardiovascular death or hospital admission for worsening heart failure, but failed to reduce all cause mortality. More than two thirds of participants were enrolled in Eastern Europe and concerns have been raised that only 89% were on beta-blockers with only 26% on optimal doses. Trials of beta-blockers in heart failure consistently show a beneficial effect on mortality. Sub-group analysis suggested that patients on 50% or more of target beta-blocker doses at baseline had no significant benefit from ivabradine for the primary endpoint of CV death or hospital admission. Further studies are needed to clarify whether ivabradine can improve outcomes when added to optimal therapy. Ivabradine (Procoralan) is not currently licensed for heart failure and should not be prescribed for this indication. It is licensed for the treatment of angina in patients in normal sinus rhythm and has been previously assessed by PACEF for this indication. It is designated RED-RED, although this is currently under review.

Reference
Swedburgh K et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *The Lancet*, early online publication, 29th August 2010 doi:10.1016/S0140-6736(10)61198-1.

Bisphosphonates and cancer risk

A retrospective observational study has suggested a possible association between oral bisphosphonate use and an increased risk of oesophageal cancer. The study

used the UK General Practice Research Database to identify people who had been diagnosed with oesophageal cancer (2954), gastric cancer (2018) or colorectal cancer (10,641) over a 10 year period and matched 5 controls for each case. There was an association between issuing of any prescription for a bisphosphonate and an increased risk of oesophageal cancer. Issuing of more than 10 bisphosphonate prescriptions was associated with an almost doubling of risk. Use over 3 years (on average 5 years) was associated with more than a doubling of the risk. The risk of oesophageal cancer did not vary by age, sex, smoking history, alcohol intake, BMI or use of PPIs, NSAIDs or steroids. No association was found between bisphosphonate use and gastric or colorectal cancers.

PACEF comment

This study suggests that bisphosphonate use may be associated with an increased risk of oesophageal cancer. The MHRA have reviewed the study and concluded that there is insufficient evidence to suggest a definite causal link; the findings of this study are not supported by other published data. The study suggests that the additional risk (if proven) is small, increasing the background risk of oesophageal cancer in people aged 60 – 79 years from 0.5 to 1 woman per 1000 and from 1.5 to 3 men per 1000 over 5 years. Patients should be advised to take bisphosphonates according to the manufacturers' instructions to minimise oesophageal damage. For alendronate 70mg once weekly, swallow whole with at least 200ml of water and remain upright for at least 30 minutes. Patients should report any symptoms of oesophageal irritation such as difficulty or pain upon swallowing, chest pain or new or worsening heartburn to their doctor.

Reference

Green J et al. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case control study within a UK primary care cohort. *BMJ* 2010; 341:c4444.

GUIDELINES FOR THE TREATMENT OF COMMONLY OCCURRING INFECTIONS IN PRIMARY CARE (WINTER 2010/11)

Updated guidelines for the treatment of commonly occurring infections in primary care have been produced and will be circulated alongside this issue of the *Bulletin*. The full text will also be accessible through the PACEF section of the NHS Lincolnshire website (see above).

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