NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 3; Number 2 **March 2009**

What's new this month:

- **PACEF have approved midazolam buccal liquid (Epistatus) for use in the emergency treatment of status epilepticus as a second line alternative to rectal diazepam (see page 2).**
- **Ivabradine (Procorolan) has not been approved for use for the symptomatic treatment of chronic stable angina (see page 4).**
- **Two new studies sheds light on a potential interaction between clopidogrel and proton pump inhibitors (see page 5).**
- **New shared care guidelines are now available on the use of azathioprine and mercaptopurine for the treatment of inflammatory bowel disease (see page 7).**
- **NICE have approved infliximab for the treatment of acute exacerbations of severely active ulcerative colitis (see page 7).**
- **NICE have approved febuxostat (Adenuric) as an option for the management of chronic hyperuricaemia in gout for people who are intolerant of allopurinol or for whom allopurinol is contraindicated (see page 7).**

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 NHS Lincolnshire 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 NHS Lincolnshire website.

SUMMARY OF PACEF DECISIONS: FEBRUARY 2009 UPDATE

Drug	Indication(s)	Traffic Light Status
Febuxostat tablets (Adenuric)	Licensed for the treatment of chronic hyperuricaemia in conditions where urate/uric acid deposition has already occurred	GREEN Should only be prescribed for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.
Icatibant injection (Firazyr)	Licensed for the symptomatic treatment of acute attacks of	RED-RED

	hereditary angioedema	
Infliximab intravenous infusion (Remicade)	For the treatment of acute exacerbations of severely active ulcerative colitis in patients in whom ciclosporin is contraindicated or clinically inappropriate.	RED
Ivabradine tablets (Procoralan)	Licensed for the symptomatic treatment of chronic stable angina in patients in normal sinus rhythm who are unable to take beta-blockers due to contra-indication or intolerance.	RED-RED
Midazolam buccal liquid (Epistatus)	Unlicensed product used for the emergency treatment of status epilepticus as a second line alternative to rectal diazepam.	AMBER Specialist initiation only; no formal shared care guideline required. N.B. This is a change to the previous RED classification.

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 LPFT **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.

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.**

RAPID DRUG ASSESSMENT

MIDAZOLAM BUCCAL LIQUID (EPISTATUS)

Midazolam buccal liquid 10mg in 1ml (Epistatus) is an unlicensed product used for the emergency treatment of status epilepticus. One multicenter randomised controlled trial (RCT) published in the *Lancet* in 2005 compared the safety and efficacy of buccal midazolam with rectal diazepam for the emergency treatment of seizures in children. Results from the trial showed that buccal midazolam was more effective than rectal diazepam in the management of acute seizures and was not associated with any increased incidence of respiratory depression. This confirmed the finding of an earlier small trial published in 1999 which concluded that buccal midazolam was at least as effective as rectal diazepam in the acute treatment of seizures and was more convenient and socially acceptable.

NICE Clinical Guideline 20 on the management of epilepsy in children and young people recommends that rectal diazepam should be used first line for the management of prolonged or repeated seizures with buccal midazolam as a second line alternative. The guidance further recommends that both treatments should be given by a trained healthcare professional or by a trained family member or carer according to an individually agreed protocol drawn up by a specialist. Although rectal diazepam is the recognised first line treatment for status epilepticus, it may not always be convenient or acceptable for medication to be administered rectally, for example in schools. Within contexts such as this, buccal midazolam often presents a more convenient and less problematic alternative. Even within the home environment, buccal administration is often preferred by parents and carers to the alternative rectal route. Both the *British National Formulary* (*BNF*) and the *BNF for Children* acknowledge buccal midazolam as a treatment option for prolonged seizures.

Midazolam buccal liquid 10mg in 1ml (Epistatus) is currently available as a manufactured special from Special Products Ltd. In common with many 'specials' it is very expensive in comparison to alternatives:

Drug	Cost per dose	Cost per pack
Buccal midazolam liquid (Epistatus)	**£13.86**	***£55.43 (4)**
Diazepam 5mg	£1.27	£6.36 (5)
Diazepam 10mg	£1.65	£8.23 (5)
Stesolid 5mg	£1.46	£7.31 (5)
Stesolid 10mg	£1.86	£9.31 (5)

(* The price quoted is if purchased direct from Special Products Ltd; the cost via a wholesaler may be greater.)

PACEF Recommendation

PACEF have approved midazolam buccal liquid (Epistatus) for use in the emergency treatment of status epilepticus as a second line alternative to rectal diazepam. Accordingly, midazolam buccal liquid 10mg in 1ml (Epistatus) is designated: AMBER. This treatment should only be used in primary care following a request from a specialist service (e.g. learning disabilities, ULH paediatrics); no formal shared care guideline is required. GPs should not feel under any obligation to respond directly to requests from carers, but should refer all such approaches back to the patient's named consultant for further consideration. Families and carers should be informed that buccal midazolam is currently unlicensed; additional training of parents or care givers will need to be given on the administration of buccal midazolam and appropriate action in the event of treatment failure. Care should be taken when prescribing midazolam buccal liquid to ensure that Epistatus is supplied as Special Products Ltd also manufacturer a larger volume product known as Consed. To avoid confusion, Epistatus should be prescribed either by brand or as buccal midazolam liquid 10mg in 1ml x 4 doses (5ml carton).

Reference: McIntyre J et al., 'Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children; a randomised controlled trial', *Lancet* 2005; 366; 205-210.

NEW DRUG ASSESSMENTS

ICATIBANT INJECTION (FIRAZYR)

Icatibant (Firazyr) is a potent, highly specific, competitive bradykinin B2 receptor antagonist licensed for the symptomatic treatment of acute attacks of hereditary angioedema. Hereditary angioedema (HAE) is a rare autosomal dominant disease that typically manifests itself as intermittent swelling in the skin, the upper airways,

the genitourinary tract and the gastrointestinal mucosa; attacks are often painful and angioedema of the upper airways can be fatal. HAE is caused by an absence or dysfunction of C1 esterase inhibitor (C1-INH), which regulates several important biological pathways, including the complement pathway and the kinin cascade. Increased levels of bradykinin are thought to be central to the clinical symptoms of HAE. The condition is relatively rare with prevalence estimated to be between 1 in 10,000 and 1 in 50,000 across the USA and Europe.

The safety and efficacy of subcutaneous icatibant have been assessed in two randomized, double-blind controlled Phase III studies; one of these studies was placebo controlled while the other used oral tranexamic acid as the comparator. In these studies, patients receiving icatibant experienced faster symptom relief than either placebo or tranexamic acid. Almost all subjects who received subcutaneous icatibant developed reactions at the site of injection including erythema, swelling, warm sensation, burning, itching and/or cutaneous pain. These reactions were generally mild in severity, transient, and resolved without further intervention.

At present, the only treatment considered comparably efficacious to icatibant is C1 esterase inhibitor injection (C1-INH) administered as an intravenous infusion. Although unlicensed in the UK and only available on a named patient basis, C1-INH injection is recommended by the British Society for Immunology Advisory Group for the treatment of acute attacks of HAE. Currently, there are no direct comparative trials between icatibant and C1-INH; icatibant injection is also substantially more expensive than C1-INH injection.

PACEF Recommendation

In the absence of comparative data against C1-INH injection, PACEF were unable to support the introduction of subcutaneous icatibant injection for the treatment of acute attacks of HAE. As a result of this, icatibant is designated RED-RED. This decision ratifies the position of ULHT Drug and Therapeutics Committee and supports the continued use of intravenous C1-INH injection for this indication.

IVABRADINE TABLETS (PROCOROLAN)

Ivabradine (Procorolan) is a selective sinus node inhibitor which decreases resting heart rate; it is licensed for the symptomatic treatment of chronic stable angina in patients in normal sinus rhythm who are unable to take beta-blockers due to contra-indication or intolerance. Clinical efficacy studies have shown that ivabradine is more effective than placebo in increasing time to angina onset and non-inferior to atenolol (50 to 100mg daily) and amlodipine (10mg daily) in increasing total exercise duration in patients with chronic stable angina. More recently, a randomized, double blind, placebo-controlled study known as the BEAUTIFUL trial set out to establish whether lowering heart rate with ivabradine reduced cardiovascular death and morbidity in patients with coronary artery disease and left ventricular systolic dysfunction. The results of the trial showed no effect of the active treatment on the primary composite end point. A further sub-group analysis confined to patients with a heart rate of 70 beats per minute (BPM) or greater failed to show any affect on a primary composite outcome including cardiovascular death or admission to hospital for new-onset or worsening heart failure. However, ivabradine did affect a secondary endpoint, by showing a reduction in admission to hospital for fatal and non-fatal myocardial infarction.

PACEF Recommendation

PACEF remain unconvinced of the benefits of ivabradine over other therapies. The results of the BEAUTIFUL study only achieve significance following sub-group analysis and scrutiny of secondary outcomes data. Comparative data against other potential alternatives such as calcium channel blockers, long-acting nitrates or nicorandil is lacking. Ivabradine is also significantly more expensive than better established alternatives. As a result of this, ivabradine is designated: RED-RED. GPs should refuse any approaches from specialists to initiate or continue the prescribing of this drug. This decision ratifies the position of ULHT Drug and Therapeutics Committee.

Reference: Kim Fox et al., 'Ivabradine for patients with stable coronary artery disease and left ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo controlled trial', *Lancet* 2008; 372; 807-16.

NEW TRIAL ASSESSMENT

POPULATION-BASED STUDY OF THE DRUG INTERACTION BETWEEN PROTON PUMP INHIBITORS AND CLOPIDOGREL

A recently published case control study in the *Journal of the Canadian Medical Association* has attempted to assess the clinical importance of a possible interaction between proton pump inhibitors (PPIs) and clopidogrel. 13,636 patients aged 66 or older (median age 76; 55.6% men) were identified from prescription, hospital discharge and insurance records from between April 2002 and December 2007 as starting clopidogrel within three days of hospital discharge following acute myocardial infarction (MI). From these records, patients were followed for 90 days after hospital discharge or until first re-admission for acute MI and 782 patients were found to have been re-admitted following a subsequent MI within 90 days; 734 of these patients were randomly matched to controls (patients at risk of a recurrent MI who had not experienced a subsequent event) and a series of analyses were undertaken to look for a possible association between the concurrent usage of a PPI and a subsequent cardiac event. The primary outcome was the rate of re-admission for acute MI in patients currently using a PPI. Secondary analyses looked at the effect of histamine H_2 – receptor antagonists, risk of recurrent MI or death within one year of discharge and risk of recurrent MI with pantoprazole alone compared with all other PPIs combined.

Following extensive multivariable adjustment and statistical analysis the results were as follows:

- The risk of re-infarction was higher in those currently taking PPIs; previous use of a PPI was not associated with any increased risk.
- The current use of pantoprazole did not increase the risk of recurrent MI; none of the other PPIs were analysed separately.
- The current use of histamine H_2 – receptor antagonists (famotidine, nizatidine and ranitidine) was not associated with re-infarction.

The results of this study suggest that patients who concurrently take PPIs with clopidogrel post-MI may be at an increased risk of further MI. A possible mechanism for this interaction has been hypothesised: clopidogrel is a prodrug that is metabolised by cytochrome P450 2C19 to its active form. Some PPIs inhibit the effects of cytochrome P450 2C19 and, as a result, may reduce the efficacy of clopidogrel. The authors suggest that pantoprazole did not show increased risk of recurrent MI as it does not inhibit cytochrome P450 2C19 and, as a result, does not prevent the metabolic activation of clopidogrel. The authors substantiate this

hypothesis using *in vitro* data comparing the effects of all five PPIs (omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole) on a range of cytochrome P450 enzymes; from this comparison lansoprazole emerges as the most potent cytochrome P450 2C19 inhibitor and pantoprazole the least potent. The extent to which this *in vitro* data is reflected *in vivo* remains in question. In addition, the US Food and Drug Administration (FDA) is currently conducting a safety review of clopidogrel in response to a number of reports indicating that genetic differences between individuals may result in clopidogrel being less effective in some people than in others.

At the time of writing, a further study published in the *Journal of the American Medical Association* has drawn similar conclusions following the retrospective analysis of a cohort of 8,205 patients discharged from hospital on clopidogrel following a diagnosis of acute MI or unstable angina. Once again concurrent PPI use with clopidogrel appears to have increased the risk of a subsequent coronary event, although the observational nature of the study means that causality cannot be confirmed.

PACEF Recommendations:

It would be premature to draw any conclusions from the findings of two studies based on observational data. Even though these studies suggest that post MI patients taking clopidogrel concurrently with a PPI are at increased risk of recurrent MI, observational data is insufficient to prove a causal relationship and further studies are required. In relation to the Canadian study, some concerns have also been raised around the failure of the study design to take into account cardiovascular risk when standardising the baseline characteristics of the case and control groups. Conclusions from the study relating to the lower risk associated with pantoprazole and the histamine H_2 – receptor antagonists arise from secondary outcomes data. The possible mechanism through which PPIs appear to inhibit the metabolism of clopidogrel derives from in vitro data only and may have limited clinical significance. The broader context of variation between individuals in the metabolism of clopidogrel due to genetic factors may be of greater significance; the FDA are currently conducting a safety review and are expected to publish their findings in the next few months. In the meantime PACEF advice is as follows:

(1) Clopidogrel should only be initiated in accordance with NICE guidance. Existing patients taking clopidogrel should be subject to regular review;

(2) Prescribers should re-evaluate the need to start or continue concurrent treatment with a PPI in patients taking clopidogrel. If the patient's risk of gastrointestinal adverse events can be reduced in any other way (e.g. through the avoidance of concomitant NSAIDs) this should be considered. If dyspepsia occurs with clopidogrel, consider a histamine H_2 – receptor antagonist such as ranitidine;

(3) Prescribers should be aware of the potential drug interaction between clopidogrel and PPIs when initiating or reviewing patients on the drug; PPIs should only be used in conjunction with clopidogrel where there is a specific indication and not for routine prophylaxis.

Further guidance will be issued by PACEF following the publication of the FDA review and any further advice from the MHRA.

References: Juurlink David N et al., 'A population-based study of the drug interaction between proton pump inhibitors and clopidogrel', *Canadian Medical Association Journal* 2009; 180 (7).
Michael Ho P et al., 'Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome', *JAMA* 2009; 301 (9): 937-44.

SHARED CARE GUIDELINES

PACEF have approved two shared care guidelines this month. These are:

- Unlicensed use of azathioprine for the treatment of inflammatory bowel disease (IBD).
- Unlicensed use of mercaptopurine for the treatment of IBD.

Copies are available from Cathy Johnson, Interface Lead Pharmacist at cathy.johnson@lpct.nhs.uk

NICE TECHNOLOGY APPRAISAL 163: *INFLIXIMAB FOR ACUTE EXACERBATIONS OF ULCERATIVE COLITIS (DECEMBER 2008)*

The key recommendations are as follows:

- **Infliximab is recommended** as an option, within its marketing authorisation, for the **treatment of acute exacerbations of severely active ulcerative colitis (UC)** only in patients in whom ciclosporin is contraindicated or clinically inappropriate based on a careful assessment of the risks and benefits of treatment of the individual patient.
- If people do not meet the criterion above, infliximab should only be used for the treatment of acute exacerbations of severely active ulcerative colitis in clinical trials.

PACEF Recommendation
Infliximab (Remicade) is designated RED for the treatment of acute exacerbations of severely active ulcerative colitis in patients in whom ciclosporin is contraindicated or clinically inappropriate.

NICE TECHNOLOGY APPRAISAL 164: *FEBUXOSTAT FOR THE MANAGEMENT OF HYPERURICAEMIA IN PEOPLE WITH GOUT (DECEMBER 2008)*

The key recommendations are as follows:

- Febuxostat (Adenuric), within its marketing authorisation, is recommended as an option for the management of chronic hyperuricaemia in gout **only** for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.
- Intolerance to allopurinol is defined as adverse effects that are sufficiently severe as to warrant either discontinuation or conservative dosing that prevents full dose escalation and the achievement of optimal effectiveness.

Febuxostat (Adenuric) is a non-purine selective inhibitor of xanthine oxidase that achieves its therapeutic effect by decreasing uric acid concentration.
It is licensed for the treatment of chronic hyperuricaemia in conditions where urate/uric acid deposition has already occurred (including a history or the presence of tophi and/or gouty arthritis).

NICE reviewed five studies as part of their appraisal. Febuxostat appears from trial evidence to be more effective at reducing serum uric acid concentration than fixed–dose allopurinol. However, fully titrated allopurinol is recommended as best practice and there is no trial evidence comparing febuxostat with a fully titrated dose schedule of allopurinol. Further evidence is required to demonstrate whether febuxostat has

any advantage over allopurinol in terms of gout flare control, reduction in tophi size and number and avoidance of longer term joint and organ damage.

As part of their appraisal, NICE have expressed concern over the increased proportion of recurrent gout flares with rebuxostat. Specialist advice has reassured them that this is likely to be linked to rate of change of serum uric acid concentration, with treatments that reduce serum uric acid concentration most effectively and rapidly having a most pronounced effect. NICE remain concerned over the higher number of cardiovascular events and deaths across the febuxostat arms of the APEX, FACT and EXCEL studies. In order to minimize this risk, the marketing authorisation for rebuxostat precludes use in patients with ischaemic heart disease and congestive heart failure.

NICE have also undertaken a cost-effectiveness analysis and retain concerns over the cost-effectiveness of febuxostat in comparison to allopurinol. As a result of all of these factors, NICE have determined that febuxostat can only be supported for NHS use as a second line therapy for the management of gout **only** in people who are intolerant of allopurinol or for whom allopurinol is contraindicated.

PACEF Recommendation

At the time of writing, febuxostat (Adenuric) has yet to be launched in the UK. Once the product becomes available, it will be designated GREEN. Febuxostat can be initiated in primary care for the treatment of chronic hyperuricaemia, but only as a second line agent in people intolerant of allopurinol or for whom allopurinol is contraindicated. Prescribers are reminded that the drug should not be used in patients with ischaemic heart disease and congestive heart failure.

NATIONAL PATIENT SAFETY AGENCY (NPSA) RAPID RESPONSE REPORT 011 – REDUCING RISK OF OVERDOSE WITH MIDAZOLAM INJECTION IN ADULTS (DECEMBER 2008)

The NPSA has identified serious problems relating to the use of midazolam for conscious sedation in adults; in the period November 2004 to November 2008 they were notified of a total of 498 incidents related to the use of midazolam (incluidng three deaths). Analysis of the reports received revealed a risk of patients receiving excessive doses of midazolam due to confusion between the high strength (5mg/ml) and low strength (2mg/ml) preparations as well as incorrect titration of dose.

The following actions are required to be implemented by 9th June:

- Ensure that the storage and use of high strength midazolam (5mg/ml in 2ml and 10ml ampoules; or 2mg/ml in 5ml ampoules) is restricted to general anaesthesia, intensive care, palliative medicine and clinical areas where its use has been formally risk assessed, for example, where syringe drivers are used.
- Ensure that in all other clinical areas, storage and use of high strength midazolam, is replaced with low strength midazolam (1mg/ml in 2ml or 5ml ampoules)
- Review therapeutic protocols to ensure that guidance on use of midazolam is clear and that the risks particularly for the elderly or frail are fully assessed.
- Ensure that all healthcare practioners involved directly or participating in sedation techniques have the necessary knowledge, skills and competences required.

- Ensure that stocks of flumazenil are available where midazolam is used and that the use of flumazenil is regularly audited as a marker of excessive dosing of midazolam.
- Ensure that sedation is covered by organisation policy and that overall responsibility is assigned to a senior clinician which in most cases will be an anaesthetist.

These recommendations relate to all healthcare areas where conscious sedation is required. This will mainly be within secondary care, but may also apply to primary care where endoscopies, minor surgery and dental procedures are carried out.

Acknowlegements

Many thanks to Cathy Johnson, Interface Lead Pharmacist, NHSL, Gill Kaylor, Prescribing Adviser, NHSL and Robyn Thompson, Senior Pharmacist from ULHT for their contributions to this edition of the *PACE Bulletin*.

Stephen Gibson,
Head of Prescribing and Medicines Management,
NHS Lincolnshire