NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 7 **May 2010**

What's new this month:

- **Paracetamol 1g tablets (Panadol OA) are not approved for use (see page 2).**
- **Prolonged release pramipexole tablets (Mirapexin Prolonged Release) are not approved for use; standard release pramipexole (Mirapexin) is approved (see page 2).**
- **NICE have issued new Clinical Guidelines on the prevention of venous thromboembolism and the treatment of unstable angina and NSTEMI (see pages 3 to 6).**
- **The MHRA have issued updated guidance on clopidogrel and PPIs (see page 8).**

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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: APRIL 2010 UPDATE

Drug	Indication(s)	Traffic Light Status
Paracetamol 1g tablets (Panadol OA)	Licensed for the relief of pyrexia and mild to moderate pain including that associated with osteoarthritis	RED-RED
Pramipexole tablets (Mirapexin)	Licensed for monotherapy or in combination with levodopa in the treatment of Parkinson's disease	GREEN
Pramipexole tablets (Mirapexin Prolonged Release)	Licensed for monotherapy or in combination with levodopa in the treatment of Parkinson's disease	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 within licensed indications**. 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: PARACETAMOL 1G TABLETS (PANADOL OA)

GlaxoSmithKline has just launched a new 1gram tablet of paracetamol known as Panadol OA; it is licensed for the relief of pyrexia and mild to moderate pain including that associated with osteoarthritis. The claimed advantage is that this double-strength paracetamol tablet will help to reduce the tablet burden for those patients on multi-component regimes experiencing compliance difficulties. The cost comparison below reveals that Panadol OA tablets are only slightly more expensive per month than standard generic 500mg tablets.

Drug	Daily dose range	Cost (£) per 100 tablets	Cost (£) per 28 days at maximum dose
Panadol OA tablets 1 gram	1 tablet up to four times daily as required.	£3.30	£3.70
Paracetamol 500mg (generic)	1-2 tabs 4-6hrly as required.	£1.62	£3.63
Paracetamol soluble	1-2 tabs 4-6hrly as required.	£4.88 (60)	£18.22
Paracetamol 500mg caps	1-2 tabs 4-6hrly as required.	£1.77 (32)	£6.02

PACEF Recommendation
PACEF are unconvinced of the benefits of a 1 gram paracetamol tablet and concerned that there may be a risk of confusion leading to accidental overdose in patients transferred from the well-established 500mg to the1 gram strength. As a result of this, paracetamol (Panadol OA) 1 gram tablets are designated RED-RED. Prescribers are reminded of the high relative cost of paracetamol 500mg capsules compared to 500mg tablets and advised to standardise prescribing around paracetamol 500mg tablets wherever possible. Paracetamol soluble tablets are significantly more expensive than standard generic paracetamol 500mg tablets and should be reserved solely for patients with swallowing difficulties. Any patient following a salt-restricted diet or hypertensive or suffering from renal impairment should avoid regular use of effervescent or soluble analgesics; the amount of sodium in non-soluble analgesics is insignificant.

RAPID DRUG ASSESSMENT: PRAMIPEXOLE PROLONGED RELEASE TABLETS (MIRAPEXIN PROLONGED RELEASE)

NICE Clinical Guideline 35: *Parkinson's disease. – Diagnosis and management in primary and secondary care* (June 2006), concluded that it was not possible to identify a preferred first-choice drug therapy for either the treatment of early Parkinson's disease (PD) or for adjuvant treatment of later disease. A number of first line treatment options for both early and later disease were advocated including pramipexole, ropinirole and rotigotine. On the basis of this, pramipexole immediate release tablets (Mirapexin®) are currently designated as GREEN.

Pramipexole prolonged release tablets (Mirapexin Prolonged Release) have recently been licensed for the treatment of Parkinson's disease either as monotherapy or in combination with levodopa. In comparison to standard release pramipexole, the prolonged release formulation is taken once daily rather than three times daily. There is no published evidence demonstrating better symptom control in comparison to immediate release pramipexole or other dopamine agonists. There may be a theoretical advantage in simplifying dosage regimes in patients experiencing compliance difficulties due to high tablet load and complicated multi-component therapy.

Direct price comparison between the standard and prolonged release products is difficult due to the range of possible dosage combinations; use of the prolonged release product does not appear to offer cost advantage over the existing standard release product. However, the patent on immediate release tablets expires in December 2010; once generic immediate release products become available, Mirapexin Prolonged Release tablets could become a costly alternative to standard therapy.

PACEF Recommendation:
Pramipexole prolonged release tablets (Mirapexin Prolonged Release) are designated RED-RED. Where pramipexole is indicated, standard release Mirapexin tablets are preferred.

NICE CLINICAL GUIDELINE 92: *VENOUS THROMBOEMBOLISM: REDUCING THE RISK OF VENOUS THROMBOEMBOLISM (DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM) IN PATIENTS ADMITTED TO HOSPITAL* (JANUARY 2010)

This new Clinical Guideline provides guidance for hospital staff on:

Assessing the risks of venous thromboembolism (VTE) and bleeding

- Assess all patients on admission to identify those who are at increased risk of venous thromboembolism (VTE).
- The risk factors for VTE risk factors which include: active cancer or cancer treatment, age (60+), critical care admission, dehydration, known thrombophilias, obesity (BMI > 30kg/m^2), one or more significant medical co-morbidities, personal history or first degree relative with a history of VTE, use of HRT, use of oestrogen containing contraceptive therapy, varicose veins with phlebitis.
- Assess all patients for risk of bleeding before offering pharmacological VTE prophylaxis. Do not offer pharmacological VTE prophylaxis to patients with any of the defined risk factors for bleeding, unless the risk of VTE outweighs the risk of bleeding.
- The risk factors for bleeding include: active bleeding, acquired bleeding disorders (e.g. acute liver failure), concurrent use of anticoagulants known to increase the risk of bleeding, lumbar puncture/epidural/spinal anaesthesia within the previous 4 hours or expected within 12 hours, acute stroke, thrombocytopenia, uncontrolled systolic hypertension, untreated inherited bleeding disorders.

Reducing the risk of VTE

- Encourage patients to mobilise as soon as possible.
- Offer pharmacological VTE prophylaxis to general medical patients assessed to be at increased risk of VTE. Choose any one of: fondaparinux sodium, low molecular weight heparin (LMWH) or unfractionated heparin (UFH) (for patients with renal failure).
- Start pharmacological VTE prophylaxis as soon as possible after risk assessment has been completed. Continue until the patient is no longer at increased risk of VTE.

Choice of mechanical VTE prophylaxis

- Base the choice of mechanical VTE prophylaxis on clinical condition, surgical

procedure and patient preference. Choose any one of: anti-embolism stockings (thigh or knee length), foot impulse devices or intermittent pneumatic compression devices (thigh or knee length).

Information for patients about VTE prophylaxis

- Before starting VTE prophylaxis, offer verbal and written information on: risks and possible consequences of VTE; importance of VTE prophylaxis and its possible side effects; correct use of VTE prophylaxis and how to reduce risk of VTE.

Anti-embolism stockings

- Do not offer anti-embolism stockings to patients with: suspected or proven peripheral arterial disease (PAD), peripheral arterial bypass grafting, peripheral neuropathy or other causes of sensory impairment, local conditions in which stockings may cause damage (e.g. fragile 'tissue paper' skin, dermatitis gangrene or recent skin graft), known allergy to material of manufacture, cardiac failure, severe leg oedema or pulmonary oedema from congestive heart failure, unusual leg size or shape and major limb deformity preventing correct fit.
- Use caution and clinical judgement when applying anti-embolism stockings over venous ulcers or wounds.
- Measure legs and use correct stocking size. Staff who fit stockings should be trained in their use and should show patients how to use them.
- Use stockings that provide graduated compression and produce a calf pressure of 14-15 mmHg.
- Encourage patients to wear the stockings day and night from admission until they no longer have significantly reduced mobility.
- Show patients how to use anti-embolism stockings correctly and ensure they understand that this will reduce their risk of developing VTE.
- Monitor use of anti-embolism stockings and offer assistance if they are not being worn correctly.

VTE prophylaxis for patients already having antiplatelet or anticoagulant therapy to treat other conditions

- Consider offering additional mechanical or pharmacological VTE prophylaxis if the patient is at risk of VTE. Take into account risk of bleeding and of co-morbidities such as arterial thrombosis.
- If the risk of VTE outweighs the risk of bleeding, consider offering pharmacological VTE prophylaxis according to the reason for admission.
- If the risk of bleeding outweighs the risk of VTE, offer mechanical VTE prophylaxis.
- Do not offer additional pharmacological or mechanical VTE prophylaxis to patients who are taking vitamin K antagonists (e.g. warfarin, acenocoumarol, phenindione) and who are within their therapeutic range, providing anticoagulant therapy is continued.
- Do not offer additional pharmacological or mechanical VTE prophylaxis to patients who are having full anticoagulant therapy (e.g. fondaparinux sodium, LMWH or UFH).

Patient information and planning for discharge

- As part of the discharge plan, offer patients and/or families or carers verbal and written information on: the signs and symptoms of deep vein thrombosis (DVT) and pulmonary embolism (PE); the correct and recommended duration of use of VTE prophylaxis at home (if discharged with prophylaxis); the signs and symptoms of adverse events

related to VTE prophylaxis (if discharged with prophylaxis); the importance of seeking help and who to contact if they have any problems using the prophylaxis (if discharged with prophylaxis); the importance of seeking medical help and who to contact if DVT, PE or another adverse event is suspected.

Flow diagrams are provided for medical patients (i.e. patients admitted for stroke, cancer, palliative care and with central venous catheters), non-orthopaedic surgery, orthopaedic surgery, major trauma or spinal injury, lower limb plaster casts, critical care and pregnancy (and up to 6 weeks post partum).

The orthopaedic surgery pathway endorses both dabigatran and rivaroxaban as previously advocated in TAs 157 and 170.

NICE CLINICAL GUIDELINES 94: *UNSTABLE ANGINA AND NON-ST-SEGMENT-ELEVATION MYOCARDIAL INFARCTION (NSTEMI)* (MARCH 2010)

This new Clinical Guideline provides guidance for hospital staff. The main recommendations are as follows:

- As soon as the diagnosis of unstable angina or NSTEMI is made, and aspirin and antithrombin therapy have been offered, formally assess individual risk of future adverse cardiovascular events using an established risk scoring system that predicts 6-month mortality (for example, Global Registry of Acute Cardiac Events [GRACE]).
- Consider intravenous eptifibatide or tirofiban as part of the early management for patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%), and who are scheduled to undergo angiography within 96 hours of hospital admission.
- Offer coronary angiography (with follow-on PCI if indicated) within 96 hours of first admission to hospital to patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%) if they have no contraindications to angiography (such as active bleeding or co-morbidity). Perform angiography as soon as possible for patients who are clinically unstable or at high ischaemic risk.
- When the role of revascularisation or the revascularisation strategy is unclear, resolve this by discussion involving an interventional cardiologist, cardiac surgeon and other healthcare professionals relevant to the needs of the patient. Discuss the choice of the revascularisation strategy with the patient.
- To detect and quantify inducible ischaemia, consider ischaemia testing before discharge for patients whose condition has been managed conservatively and who have not had coronary angiography.

Before discharge offer patients advice and information about:

- their diagnosis and arrangements for follow-up (in line with NICE CG 48 *MI: secondary prevention*).
- cardiac rehabilitation (in line with NICE CG 48 *MI: secondary prevention*).
- management of cardiovascular risk factors and drug therapy for secondary prevention (in line with NICE CG 48 *MI: secondary prevention* and NICE CG 67 *Lipid modification*)
- lifestyle changes (in line with NICE CG 48 *MI: secondary prevention*).

Early management of unstable angina and NSTEMI

- Offer a single loading dose of 300mg aspirin and continue aspirin indefinitely.
- Offer fondaparinux to patients without a high bleeding risk unless angiography is planned within 24 hours.
- Offer unfractionated heparin (UFH) if angiography is likely within 24 hours.
- Carefully consider choice and dose of antithrombin for patients with a high bleeding risk.

- Consider UFH with dose adjusted to clotting function if creatinine > 265 micromoles per litre.

Antiplatelet therapy

Aspirin

- Offer to all patients unless contraindicated and continue indefinitely.
- Offer a single 300mg loading dose.
- Consider clopidogrel monotherapy for patients with aspirin hypersensitivity.

Clopidogrel

- Offer a 300mg loading dose to patients with a predicted 6 month mortality of more than 1.5% and no contra-indications (such as excessive bleeding risk).
- Offer a 300mg loading dose to all patients with no contraindications who may undergo PCI within 24 hours of admission.
- After a single 300mg loading dose clopidogrel should be continued at 75mg daily for 12 months.
- Consider stopping clopidogrel 5 days before CABG in patients with low risk.
- For patients at intermediate or higher risk, discuss continuing clopidogrel before CABG with the cardiac surgeon. Base the decision on the balance of ischemic and bleeding risk.

PACEF Recommendations:
Prescribers are reminded of standard PACEF advice on the use of generic clopidogrel: In order to maximise cost-effectiveness, prescribers are strongly recommended to ensure that all prescribing of clopidogrel is for clopidogrel tablets 75mg, clopidogrel besilate tablets 75mg or clopidogrel hydrochloride tablets 75mg. Prescribing of generic clopidogrel hydrogen sulphate tabs 75mg or Plavix for any indication is no longer recommended.
At present the basic NHS reimbursement price for generic clopidogrel 75mg tablets is £10.90 for 30; clopidogrel hydrogen sulphate tablets 75mg (Plavix) cost £35.64 for 30.

Glycoprotein IIb/IIIa inhibitors

- Consider eptifibatide or tirofiban for patients at intermediate or higher risk if angiography is scheduled within 96 hours of admission.
- Consider abciximab as an adjunct to PCI for patients at intermediate or higher risk who are not already receiving a GPI.

Antithrombin therapy

- Offer fondaparinux to patients without a high bleeding risk unless angiography is planned within 24 hours.
- Offer UFH as an alternative to fondaparinux if angiography is likely within 24 hours of admission.
- Carefully consider choice and dose of antithrombin for patients with a high bleeding risk.
- Consider UFH with dose adjusted to clotting function if creatinine > 265 micromoles per litre.
- Offer systemic UFH (50-100 units/kg) in the cardiac catheter laboratory to patients in fondaparinux who are undergoing PCI.
- As an alternative to the combination of a heparin plus a GPI, consider bivalirudin for patients undergoing PCI who are at intermediate or higher risk and are not already on a GPI or fondaparinux.

Assessing left ventricular function

- Assess left ventricular function in all patients who have had an MI or with unstable angina.

NEW TRIALS IN BRIEF

Antipsychotic use in elderly patients

In this study a Dutch primary care database was used to identify people aged 65 years or older who used an antipsychotic from 1996 to 2006. 258 cases of community acquired pneumonia were matched to 1686 controls. Current use of atypical or typical antipsychotics was associated with a dose-dependent increase in the risk of pneumonia compared with past use of antipsychotic drugs. Atypical antipsychotics were associated with an increase in the risk of fatal pneumonia.

PACEF Comment:
This study supports other observational data suggesting that antipsychotic use in the elderly may be associated with an increased risk of pneumonia. Current advice is that prescribers should avoid using antipsychotics for non-cognitive symptoms in dementia because of an increased risk of stroke and death unless the patient is severely distressed or there is an immediate risk of harm to themselves or others. If antipsychotics are prescribed within this context, regular review is recommended.

Reference:
Trifiro G et al. Association of community acquired pneumonia with antipsychotic drug use in elderly patients: a nested case control study. *Ann Int Med* 2010; 152: 418 – 425.

Blood pressure control in type 2 diabetes

A randomised controlled trial of 4733 people with type 2 diabetes randomised to either intensive BP control (systolic < 120mmHg, mean achieved 119.3) or standard BP control (<140mmHg, mean achieved 133.5) with a mean follow up of 4.7 years. No difference was identified between the two treatment groups in the primary outcome, a composite of non-fatal MI, non-fatal stroke or cardiovascular death.

PACEF Comment:
Reducing BP in type 2 diabetics to significantly below currently recommended targets does not appear to improve outcomes.

Reference:
ACCORD Writing Group, Effects of intensive blood pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010 (10.1056/NEJMoa1001286) published online 14/3/10

Compliance with bisphosphonates

Using data from a United States health insurance database the impact of dosing schedules on compliance with bisphosphonates during the first year of use was assessed using the medication possession ratio. 61,125 users of bisphosphonates (n=1034 daily, n=56,925 weekly and n=3166 monthly) were indentified. 49% of monthly users had a medication possession ratio of >80%, compared with 49% of weekly users and 23% of daily users.

PACEF Comment:
Prescribers are reminded that monthly ibandronate (Bonviva) 150mg tablets are not recommended for use due to weaker evidence of non-vertebral and hip fracture reduction, greater cost and lack of evidence of cost-effectiveness (Designation RED-RED). This study reinforces this recommendation. There is no evidence that compliance is any better with monthly bisphoshonates than weekly bisphosphonates. The relatively poor concordance with bisphosphonates in the first year of use in this study is notable and is consistent with other data.

Reference:
Briesacher B.A. et al. Adoption of once monthly oral bisphosphonates and the impact on adherence. *Am J Med* 2010; 123(3): 275 - 280

Non-Steroidal Anti-Inflammatory Drugs and cardiovascular risk

A prospective case control study of almost 3,000 patients hospitalised with acute coronary syndrome (ACS) in Spain with a similar number of age matched controls to study the risk of ACS associated with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Overall the risk of ACS was not increased by current NSAID use; an increased risk of ACS was associated with use of high dose NSAIDs and in those with a history of ischaemic heart disease. Most of the observed increased risk with NSAIDs was due to an increased risk of non-STEMI.

PACEF Comment:
This study supports other observational data that suggest an increased risk of thrombotic events associated with NSAID use at high doses and for long periods. PACEF has previously recommended that oral NSAIDs and coxibs should be used at the lowest effective dose for the shortest duration, and has highlighted the possible increased thrombotic risk (*PACE Bulletin* May 2008 2(7): 2)

Reference:
Bueno H et al. Use of non-steroidal anti-inflammatory drugs and type-specific risk of acute coronary syndrome. *Am J Cardiol*. 2010; 105(8):1102 – 1106.

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

Yasmin: update on risk of venous thromboembolism (VTE)

- Recently published studies suggest that the risk of VTE (including deep vein thrombosis and pulmonary embolism) in association with the combined oral contraceptive (COC) Yasmin may be slightly higher than previously estimated.
- The risk is somewhere between that associated with COCs containing levonorgestrel ('second generation' pills) and those containing desogestrel or gestodene ('third generation' pills).
- The risk of VTE with Yasmin remains very small and lower than that associated with pregnancy.
- Prescribers should be aware of this new evidence when discussing the most suitable type of contraception for a woman who wants to start or switch contraception.

Clopidogrel and proton pump inhibitors: Interaction – updated advice

- In May 2009 the EU Committee for Medicinal products for Human Use (CHMP) discouraged the concomitant use of PPIs and clopidogrel unless absolutely necessary. This advice was based on a number of observational studies that suggested that PPIs may reduce the effectiveness of clopidogrel by reducing conversion to its active form.
- Two studies completed at the end of August 2009 confirmed that omeprazole can reduce levels of the active form of clopidogrel in the blood and reduce its antiplatelet effects. **The CHMP have concluded that there is an interaction between clopidogrel and omeprazole; there is also some evidence of a similar interaction with esomeprazole. There is no evidence to support the extension of this warning to other PPIs**
- In light of the most recent evidence, previous advice on the concomitant use of clopidogrel and PPIs has now been modified.
- **Use of either omeprazole or esomeprazole with clopidogrel should be discouraged.**
- Current evidence does not support extending this advice to other PPIs.

Advice for healthcare professionals

- Concomitant use of clopidogrel and omeprazole or esomeprazole is to be discouraged unless considered essential.
- Doctors should check whether patients who are taking clopidogrel are also buying OTC omeprazole and consider whether other GI therapies would be more suitable.

- Pharmacists should check whether patients buying omeprazole are also taking clopidogrel.
- Consider PPIs other than omeprazole or esomeprazole in patients taking clopidogrel. Other GI therapy (e.g. H2 blockers (except cimetidine)) or antacids may be more suitable in some patients.
- Discourage concomitant use of other known CYP2C19-inhibiting medicines with clopidogrel ; these are expected to have a similar effect to omeprazole and esomeprazole.
- CYP2C19 inhibitors include fluvoxamine, fluoxetine, moclobemide, voriconazole, fluconazole, ticlopidine, ciprofloxacin, cimetidine, carbamazepine, oxcarbazepine and chloramphenicol.

PACEF Recommendations

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

(2) Prescribers should be aware of the potential drug interaction between clopidogrel and omeprazole or esomeprazole when initiating or reviewing patients on clopidogrel. Omeprazole and esomeprazole should only be used in conjunction with clopidogrel in exceptional circumstances.

(3) Patients currently receiving clopidogrel in combination with either omeprazole or esomeprazole should be identified with a view to stopping or changing the PPI. If dyspepsia occurs with clopidogrel, consider an alternative PPI such as lansoprazole or ranitidine or an antacid.

Intravenous zoledronic acid; adverse effects on renal function

- Zoledronic acid is associated with reports of renal impairment and renal failure, especially in patients with pre-existing renal dysfunction or other risk factors.
- Renal function should be measured before each dose and patients should be adequately hydrated before treatment.
- Renal function monitoring is recommended after use of zoledronic acid in at-risk patients – especially those with pre-existing renal impairment.
- Use in patients with severe renal impairment is generally not recommended, but may be considered for tumour-induced hypercalcaemia, if the benefits outweigh the risks.

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