NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 3; Number 10 **October 2009**

What's new this month:

- **New generic clopidogrel products are now available (see page 3).**
- **Hydrogen peroxide 1% cream (Crystacide) has not been approved for use (see page 4).**
- **Ibandronic acid 150mg tablets (Bonviva) once monthly 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 (see page 4)**
- **Aspirin prolonged release 162.5mg capsule (Flamasacard) has not been approved for use (see page 6).**
- **Glucophage Powder is approved for use for patients with swallowing difficulties requiring metformin as a liquid formulation. Metformin oral solution 500mg in 5ml is no longer recommended apart from in exceptional circumstances (see page 6).**
- **Aspirin for primary prevention of cardiovascular disease is reviewed (see page 8)**
- **NICE have approved lenalidomide (Revlimid) for the treatment of multiple myeloma in people who have received at least one prior therapy (see page 9)**
- **NICE have issued clinical guidelines on the diagnosis, assessment and management of diarrhoea and vomiting in children (see page 10)**
- **Further guidance is given on interaction between clopidogrel and proton pump inhibitors (see page 12)**
- **Legal clarification is provided around the issue of patient consent as it applies to the implementation of therapeutic switch programmes in practice (see page 13)**

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. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS Lincolnshire website (www.lpct.nhs.uk).

SUMMARY OF PACEF DECISIONS: JULY 2009 UPDATE

Drug	Indication(s)	Traffic Light Status
Alendronate 70mg tabs (generic)	Treatment of postmenopausal osteoporosis.	GREEN First line bisphosphonate of choice in both the primary and secondary prevention of postmenopausal osteoporosis (subject to NICE criteria)
Aspirin prolonged release capsules 162.5mg (Flamasacard)	Licensed for secondary prophylaxis after a first coronary or cerebrovascular ischaemic event and following coronary angioplasty or coronary artery bypass surgery where rapid onset of action is not required.	RED-RED
Cetuximab intravenous infusion (Erbitux)	Treatment of recurrent and/or metastatic squamous cell cancer of the head and neck.	RED-RED
Hydrogen peroxide 1% cream (Crystacide)	Licensed for the treatment of primary and secondary superficial skin infections.	RED-RED
Ibandronic acid 50mg tablets (Bondronat)	Licensed for the reduction of bone damage in bone metastases in breast cancer	AMBER Shared care guideline available
Ibandronic acid 150mg tablets (Bonviva)	Treatment of postmenopausal osteoporosis.	RED-RED
Lenalidomide (Revlimid) capsules	Licensed in combination with dexamethasone for the treatment of multiple myeloma	RED Should be considered as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies.
Metformin powder for oral solution 500mg and 1000mg (Glucophage Powder)	Type 2 diabetes , particularly in overweight patients, when diet and exercise provide inadequate control	GREEN N.B. Can be used second line in those unable to swallow standard release generic metformin tablets or sustained release metformin tablets. Should be used in preference to the more costly metformin oral solution
Risedronate 35mg tabs (Actonel Once a Week)	Treatment of postmenopausal osteoporosis.	GREEN Second line alternative bisphosphonate in patients who are unable to take, intolerant or contra-indicated to alendronate in both the primary and secondary prevention of postmenopausal osteoporosis

		(subject to NICE criteria).

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/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**. 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.**

LAUNCH OF GENERIC CLOPIDOGREL

Prescribers will already be aware of the launch of generic clopidogrel in the UK. In addition to the existing product, **clopidogrel hydrogen sulphate tablets (Plavix)**, two new generic salts, **clopidogrel hydrochloride tablets** and **clopidogrel besilate tablets,** are also now available. All of these preparations are licensed for the prevention of atherothrombotic events in adults suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. All of the generic companies have successfully demonstrated bioequivalence to clopidogrel hydrogen sulphate (Plavix) in order to gain a license. However, only Plavix holds an additional license for the treatment of acute coronary syndrome in combination with aspirin and this indication is patent protected.

As you will be aware, Sanofi-Aventis have written to all prescribers urging them to specify either clopidogrel hydrogen sulphate or brand name Plavix on all prescriptions for combination treatment with aspirin for acute coronary syndrome. This strategy is likely to both protect the Sanofi-Aventis market share and prevent the realisation of generic savings related to generic clopidogrel. At present, the new generic salts of clopidogrel are reimbursed at slightly less than the originator brand (Plavix), but in the coming months this may change radically if generic clopidogrel moves into Category M and prices begin to fall. In the medium term, large-scale switching of all ACS patients to Plavix is likely to reduce dramatically the savings that will result from falling reimbursement prices of low cost generic clopidogrel.

Where a particular salt is specified on a prescription, community pharmacies are obliged, both legally and ethically, to supply that salt; for open prescriptions for

clopidogrel 75mg tablets, any salt may be dispensed. Community pharmacists have been advised by the Pharmaceutical Services Negotiating Committee (PSNC) to take into account licensing variances when dispensing clopidogrel. This may result in pharmacists contacting prescribers to clarify the indication for which the drug is to be supplied.

PACEF Recommendation:
PACEF is currently considering options around our future clopidogrel prescribing policy. One option is to develop a local policy for off-label use of generic clopidogrel for all indications. We are currently seeking further advice from the MHRA and will issue definitive advice to all prescribers shortly. In the meantime, we do not recommend any change to existing prescriptions.

RAPID DRUG ASSESSMENT: HYDROGEN PEROXIDE 1% CREAM (CRYSTACIDE)

Hydrogen peroxide 1% cream (Crystacide) is an antiseptic agent licensed for the treatment of primary and secondary superficial skin infections. This product was assessed by PACEF as a possible alternative to topical antibiotic preparations in the treatment of common skin infections such as impetigo. At present, the most widely prescribed topical antibiotic preparation is fusidic acid 2% cream/ointment (Fucidin). However, bacterial resistance among *Staphylococcus* isolates to fusidic acid is on the increase; current advice from the Health Protection Agency (HPA) recommends the restriction of topical antibiotic preparations to localised lesions only.

PACEF reviewed the trial evidence for hydrogen peroxide cream 1% (Crystacide) and found it to be extremely limited. The only published trial involves the use of an alternative brand of hydrogen peroxide in impetigo; these results may not be directly transferable from one product to another. A recent review published in the *Drug and Therapeutics Bulletin* continues to advocate topical fusidic acid for 7 days as the recommended first line treatment for impetigo. Both the HPA and a recent NHS Clinical Knowledge Summary recommend that first line treatment for impetigo should be topical fusidic acid; neither advocate the use of topical antiseptic preparations such as hydrogen peroxide. Hydrogen peroxide 1% cream (Crystacide) is also approximately twice the price of better established first line alternatives.

PACEF Recommendation:
Fusidic acid 2% cream/ointment remains the first line treatment of choice for impetigo. Hydrogen peroxide 1% cream (Crystacide) is not recommended for use. Designation: RED-RED.

References

1. Health Protection Agency, *Management of Infection Guidance for Primary Care - for consultation and local adaptation* (June 2008).
2. NHS Clinical Knowledge Summaries: *Impetigo* (June 2009).
3. Christensen OB, Anehus S., Hydrogen peroxide cream: an alternative to topical antibiotics in the treatment of impetigo contagiosa. *Acta Dermato-Venereologica* Vol 74 issue 6, 460-2. (Nov 1994) from Cochrane Central Register of Controlled Trials.
4. *Drug & Therapeutics Bulletin* Treating impetigo in primary care. Vol 45 No 1 (January 2007).

RAPID DRUG ASSESSMENT: IBANDRONIC ACID 150MG TABLETS (BONVIVA)

In a recent issue of the *PACE Bulletin* (Volume 2, No 19 (December 2008)), we reviewed NICE Technology Appraisals 160 and 161 on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women. As you will remember, NICE recommended alendronate 70mg once weekly as the first line

treatment of choice, subject to the patient meeting certain criteria. Beyond alendronate and subject to further criteria, risedronate or etodronate were advocated second line. Although TAs 160 and 161 covered many of the treatments currently available, ibandronate 150mg tablets (Bonviva) were not included. In order to fill this gap in local guidance, PACEF have reviewed the evidence base for Bonviva.

Ibandronic acid tablets 150mg (Bonviva) are licensed for the treatment of postmenopausal osteoporosis. In contrast to other daily and weekly bisphosphonate regimens, ibandronic acid 150mg is given as a once monthly dose. This is claimed by the manufacturer to improve compliance and reduce adverse events. Evidence for this is largely derived from two patient preference studies comparing once weekly alendronate to once monthly ibandronate that have identified improved concordance and greater patient preference with monthly ibandronate. In addition, increasing the dose interval of ibandronate to weekly or monthly does not seem to change the incidence of gastro-intestinal adverse effects when compared with daily dosing of alendronate, risedronate or ibandronate.

A review of the evidence base for key osteoporosis treatments undertaken as part of the preparation of the recently published National Osteoporosis Guideline summarizes the evidence for vertebral, non-vertebral and hip fracture reduction as follows:

	Vertebral	Non-vertebral	Hip
alendronate	A	A	A
ibandronate	A	A[1]	nae
risedronate	A	A	A
zolendronate	A	A	A
raloxifene	A	nae	nae
strontium	A	A	A[1]
teriparatide	A	A	nae
Para-thyroid hormone	A	nae	nae

Key
A – High quality evidence
A[1] – evidence obtained from post-hoc analysis only
nae – not adequately evaluated

From this it can be concluded that the best evidence for fracture reduction is for alendronate, risedronate and zolendronate; the evidence for ibandronate is weaker or not available for non-vertebral and hip fracture reduction. Hence, although some people may prefer a monthly approach to treatment, the quality of evidence supporting the selection of ibandronate is inferior to preferred first line/second line alternatives such as alendronate and risedronate. Specifically, the evidence base around the 150mg dose is relatively weak. A single non-inferiority trial was identified that compared different doses of ibandronate, including 150mg monthly, over a period of two years in 1,290 patients, but with no alternative bisphosphonate or placebo arm. The trial showed non-inferiority of monthly treatment to daily ibandronate treatment.

A cost comparison reveals the following:

Drug	**Dose**	**Cost (£) pa**
ibandronate	150mg monthly	£239.20
alendronate	70mg weekly	£20.28

risedronate	35mg weekly	£253.63

PACEF Recommendation:
Alendronate 70mg once weekly, as advocated by NICE, remains our preferred first line bisphosphonate of choice in terms of efficacy, safety and cost-effectiveness. Risedronate 35mg once weekly is a suitable alternative for patients intolerant of alendronate subject to the application of NICE second line treatment criteria. Ibandronic acid 150mg tablets (Bonviva) once monthly 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. As a result of this, ibandronic acid 150mg tablets (Bonviva) are designated RED-RED. No new patients should be initiated on this bisphosphonate; existing patients should be considered for a therapeutic switch to generic alendronate 70mg once weekly where appropriate. Prescribers are referred to *PACE Bulletin* (Volume 2, No 19 (December 2008) for further guidance. Please note that this guidance does not apply to ibandronic acid 50mg tablets (Bondronat) which have been approved for shared care for the reduction of bone damage associated with metastic bone disease as a result of advanced breast cancer. Designation: AMBER (a shared care guideline is available)

References

1. National Osteoporosis Guideline Group (NOGG), *Guideline for the diagnosis and management of osteoporosis – in postmenopausal women and men from the age of 50 years in the UK.*
2. Regional Drug and Therapeutics Centre Drug Update. *Which Bisphosphonate- for osteoporosis?*. January 2008. www.nyrdtc.nhs.uk.
3. London New Drugs Group APC/DTC Briefing Document. *Comparison of bisphosphonates and strontium ranelate for osteoporosis.* May 2007.

RAPID DRUG ASSESSMENT: ASPIRIN PROLONGED RELEASE CAPSULES 162.5MG (FLAMASCARD)

Flamasacard is a prolonged-release 162.5mg formulation of aspirin licensed for secondary prophylaxis after a first coronary or cerebrovascular ischaemic event and following coronary angioplasty or coronary artery bypass graft. An aspirin dose of 162.5mg has been used in some trials notably ISIS-2, but is more commonly used in the USA where standard aspirin strength is 325mg. A meta-analysis conducted by the Antithrombotic Trialist's Collaboration has shown that daily doses of aspirin ranging from 75mg to 325mg appear to be equally effective in terms of their antiplatelet effect. They conclude that, in terms of long-term prevention of serious vascular events in high risk patients, a daily dose in the range of 75mg-150mg should be effective.

A further systematic review published in the *Journal of the American Medical Association* (*JAMA*) examined the relationship between aspirin doses and their efficacy and safety. Doses ranged from 30mg daily to 1300mg; the most frequently used preparations in the USA are either 81mg or 325mg. The review concluded that whilst most patients would benefit from initial larger doses of either 160-325mg for rapid inhibition of platelet COX- 1, longer term treatment should be for lower doses (e.g.75mg) as adverse effects are dose-related.

A cost comparison reveals the following:

Drug	Daily dose	Cost (£) pa
Aspirin prolonged release 162.5mg capsule	162.5mg	£32.76

(Flamasacard)		
Aspirin dispersible 75mg tablets	75mg 2x 75mg	£10.66 £21.32
Aspirin gastro-resistant 75mg tablets	75mg 2x 75mg	£12.22 £24.44
Nu-Seals Aspirin 75mg tablets	75mg 2 x 75mg	£20.28 £40.56

PACEF Recommendation:
Within the UK, the recognised dose of aspirin for secondary prevention of cardiovascular disease is 75mg daily increasing to 150mg (if required). PACEF can see no compelling reason to advocate change from standard UK doses to standard USA doses. As a result of this, aspirin prolonged release 162.5mg capsule (Flamasacard) is designated RED-RED.

RAPID DRUG ASSESSMENT: METFORMIN 500MG AND 1000MG POWDER FOR ORAL SOLUTION (GLUCOPHAGE POWDER)

Metformin is now well established as the first line treatment of choice for type 2 diabetes mellitus. However, some patients have problems swallowing standard or modified release tablets and have to take metformin in the form of an oral solution. Metformin oral solution 500mg in 5ml is available as a licensed product, but is prohibitively expensive. **Recently launched metformin powder for oral solution sachets 500mg and 1000mg (Glucophage Powder) are much less costly than the oral solution and present a more cost-effective alternative for most patients with swallowing difficulties.** A cost comparison illustrates the point:

Drug	Strength	Cost
Metformin powder for oral solution (Glucophage Powder)	500mg	£3.29 (30's) £6.58 (60's)
Metformin powder for oral solution (Glucophage Powder)	1000mg	£6.58 (30's) £13.16 (60's)
Metformin oral solution	500mg/5ml	£62.03 (100ml)
Metformin tablets	500mg	£0.95 (28's) £1.39 (84's)
Metformin S.R tablets (Glucophage SR)	500mg m.r	£3.07 (28's) £6.14 (56's)

PACEF Recommendation:
Where indicated, standard release generic metformin tablets should be prescribed first line in the treatment of type 2 diabetes mellitus. Glucophage Powder for oral solution is more expensive than standard release metformin tablets, but offers an alternative for patients with swallowing difficulties. It should be used in preference to the more costly metformin oral solution 500mg in 5mlwherever possible. Prescribers are urged to utilize the range of alternative metformin formulations to enable as many people to benefit from metformin as possible. Glucophage Powder is designated GREEN for patients requiring metformin as a liquid formulation. Metformin oral solution 500mg in 5ml is not recommended for use apart from in exceptional circumstances (i.e. where the 500mg and 1000mg strengths of Glucophage Powder cannot be readily utilised to deliver the patient's required dose). Prescribers should consider moving existing patients from metformin oral solution to Glucophage Powder wherever practical.

NEW TRIALS IN BRIEF

INCREASED HOSPITAL-ACQUIRED PNEUMONIA RISK IN PATIENTS TAKING ACID SUPPRESSIVE MEDICATION

This is a prospective pharmaco-epidemiologic cohort study of adults admitted to a large US hospital (excluding ICU) over a 3 year period including more than 63,000 admissions. Acid suppressive medications (Histamine 2 Receptor Antagonists (H2RAs) and Proton Pump Inhibitors (PPIs)) were associated with a 30% increased odds of hospital acquired pneumonia. In a subset analyses, statistically significant risk was demonstrated only for PPI use.

PACEF Comment:
As reported in a previous issue of the *PACE Bulletin* (Volume 2, No 19 (December 2008)), the use of PPIs and H2RAs has also been suggested as a risk factor for the development of Clostridium difficile associated disease. It would seem prudent to regularly review long-term H2RA and PPI use and to avoid long-term use where possible.

Reference
Herzig SJ et al. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009;301(20):2120-2128

COST EFFECTIVENESS OF PRESCRIBING PPIS WITH NSAIDS OR COX-II INHIBITORS

This analysis uses an economic model to estimate the impact of different treatment options for osteoarthritis taking into account effectiveness and adverse events. The model found that once the costs of treating adverse effects are taken into account, adding a low cost PPI to a NSAID or Cox-2 inhibitor is cost effective even for low risk patients aged 55 years and over. The degree of uncertainty around the cost-effectiveness of adding a PPI to a Cox-2 inhibitor is high.

PACEF Recommendation:
Prescribers are reminded of existing PACEF advice from *PACE Bulletin* Vol 2, No 7 (May 2008). PACEF recommend that all repeat and ongoing oral NSAID and Cox-2 inhibitor prescribing in people aged 55 and over should be supported with a concurrent PPI. Either generic lansoprazole capsules (recommended dose 15mg to 30mg daily) or generic omeprazole capsules (recommended dose 20mg daily) should be prescribed. These recommendations do not extend to acute or infrequent scripts.

Reference
Latimer N et al. Cost effectiveness of COX 2 selective inhibitors and traditional NSAIDs alone or in combination with a proton pump inhibitors for people with osteoarthritis. *BMJ* 2009; 339:b2538 doi:10.1136/bmj.b2538

ASPIRIN FOR PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS

In the last *PACE Bulletin* we briefly reviewed this meta-analysis of participants in 6 primary prevention trials of low dose aspirin and 16 secondary prevention trials. In the primary prevention trials, aspirin reduced serious vascular events by 12% (0.51% aspirin vs. 0.57% control per year, p=0001). This was mainly due to a reduction in non-fatal myocardial infarction (MI). There was no significant difference in the risk of strokes and vascular mortality. Aspirin was associated with increased gastrointestinal

and extracranial bleeds (0.10% aspirin vs. 0.07% control per year, p<0.0001). Without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against the increased risk of major bleeds.

These figures equate to a Number Needed to Treat (NNT) of 1667 for one year to prevent a serious vascular event compared to a Number Needed to Harm (NNH) of 3334 for major gastrointestinal or extra-cranial bleeds in 1 year. **Alternatively, for every 10,000 people treated with aspirin there were 7 fewer cardiovascular events and 1 extra haemorrhagic stroke and 3 extra gastrointestinal bleeds each year.**

In addition to this, the aspirin trials included were mainly in people not taking statins. Statins would further reduce the risk of cardiovascular events and so the absolute benefits of aspirin in patients taking statins would be less than reported in this meta-analysis. The authors suggest that the absolute benefit of adding aspirin could be about half as large as suggested by their meta-analysis. If this is the case, the benefits and hazards of aspirin could be of a similar magnitude.

PACEF Recommendation

Prescribers are reminded of existing PACEF advice. There are an increasing number of complementary trials that suggest that existing assumptions around the potential benefits of aspirin in the primary prevention of cardiovascular (CV) disease may be flawed. Following a review of the Prevention of Progression of Arterial Disease and Diabetes trial (POPADAD), PACEF concluded that diabetics without CV disease who are experiencing harm, or are likely to experience harm from aspirin could reasonably discontinue aspirin since the risks were likely to exceed any possible benefits. The Antithrombotic Trialists' Collaboration meta-analysis of aspirin in primary prevention of CVD raises wider concerns beyond the diabetic population. When prescribing aspirin for primary prevention, the small absolute reduction in some CV outcomes should be weighed against a possible increase in major bleeds. The decision to prescribe should be made on an individual patient basis. Patients already experiencing dyspepsia (which may require symptomatic treatment) or at high gastrointestinal risk may experience more harm from aspirin than benefit. Where large multi-component prescriptions are subject to review and rationalisation, priority should be given to evidence based interventions such as statins and antihypertensive agents. PACEF will continue to keep this issue under review and update guidance accordingly.

Reference

Antithrombotic Trialists' Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *The Lancet* 2009; 373: 1849 – 1860. doi:10.1016/S0140-6736(09)60503-1

NICE TECHNOLOGY APPRAISAL 171: *LENALIDOMIDE FOR THE TREATMENT OF MULTIPLE MYELOMA IN PEOPLE WHO HAVE RECEIVED AT LEAST ONE PRIOR THERAPY* (JUNE 2009)

The key recommendations are as follows:

- Lenalidomide in combination with dexamethasone is recommended, within its licensed indication, as an option for the treatment of multiple myeloma only in people who have received two or more prior therapies, with the following condition: The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days;

normally a period of 2 years) will be met by the manufacturer. This is known as the 'patient access scheme'.
- People currently receiving lenalidomide for the treatment of multiple myeloma, but who have not received two or more therapies should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

PACEF Recommendation:
Lenalidomide (Revlimid) is designated as RED for the treatment of multiple myeloma, but only in people who have received two or more prior therapies.

NICE TECHNOLOGY APPRAISAL 172: *CETUXIMAB FOR THE TREATMENT OF RECURRENT AND/OR METASTATIC SQUAMOUS CELL CANCER OF THE HEAD AND NECK* (JUNE 2009)

The key recommendations are as follows:

- Cetuximab in combination with platinum-based chemotherapy is not recommended for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck.
- People currently receiving cetuximab in combination with platinum-based chemotherapy for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck should have the option to continue treatment until they and their clinician consider it appropriate to stop.

PACEF Recommendation:
Cetuximab (Erbitux) is designated RED-RED for the treatment of recurrent and/or metastatic squamous cell cancer of the head and neck.

NICE CLINICAL GUIDELINE 84: *DIARRHOEA AND VOMITING IN CHILDREN* (APRIL 2009)

The key recommendations are as follows:

Diagnosis
- Suspect gastroenteritis if there is a sudden change to loose or watery stools or onset of vomiting.
- Perform stool microbiological investigations if: septicaemia is suspected **or** there is blood and/or mucus in the stool **or** the child is immunocompromised.

Assessing dehydration and shock
- Signs and symptoms of clinical dehydration include: altered responsiveness (e.g. irritable, lethargic), decreased urine output, sunken eyes, dry mucous membranes (except 'mouth breathers'), tachycardia, tachypnoea, reduced skin turgor.
- Signs and symptoms of clinical shock include: decreased level of consciousness, pale or mottled skin, cold extremities, tachycardia, tachypnoea, weak peripheral pulses, prolonged capillary refill time, hypotension.

Fluid management
- In children with gastroenteritis but without clinical dehydration: continue breastfeeding and other milk feeds; encourage fluid intake; discourage fruit juices and carbonated drinks (especially in those at increased risk of dehydration); **offer oral rehydration salt solution (ORS) to those at increased risk of dehydration.**

- **In children with clinical dehydration, including hypernatraemic dehydration: use low-osmolarity ORS solution (240-250mOsm/l) for oral rehydration therapy (i.e. Dioralyte, Dioralyte Relief, Electrolade and Rapolyte); give 50ml per kg for fluid deficit replacement over 4 hours as well as maintenance fluid; give the ORS solution frequently and in small amounts; consider supplementation with usual fluids (including milk feeds or water, but not fruit juice or carbonated drinks) if they refuse to take sufficient quantities of ORS solution and do not have red flag signs (i.e. deteriorating, altered responsiveness, sunken eyes, tachycardia, tachypnoea, reduced skin turgor); monitor the response to ORS therapy by regular clinical assessment.**

Nutritional management

During rehydration therapy:

- Continue breastfeeding.
- Do not give solid foods.
- For children without red flag signs do not routinely give oral fluids other than ORS solution; consider supplementing with usual fluids (e.g. milk feed or water, but not fruit juice or carbonated drinks) if they consistently refuse ORS solution.
- For children with red flag signs do not give oral fluids other than ORS solution.

After rehydration

- Give full-strength milk straight away.
- Reintroduce the child's usual solid food.
- Avoid giving fruit juices/carbonated drinks until the diarrhoea has stopped.

Information and advice for parents and carers

- Washing hands with soap (liquid if possible) in warm running water and careful drying are the most important factors in preventing the spread of gastroenteritis.
- Hands should be washed after going to the toilet or nappy changes and before preparing, serving or eating food.
- Towels used by infected children should not be shared.
- Children should not attend any school or childcare facility while they have diarrhoea or vomiting.
- Children should not go back to school or other childcare facility until at least 48 hours after the last episode of diarrhoea or vomiting.
- Children should not swim in swimming pools for 2 weeks after the last episode of diarrhoea.

Advice to prescribers

- **Do not give antidiarrhoeals.**
- **Do not routinely give antibiotics.**

Give antibiotics to children:

- With suspected or confirmed septicaemia.
- With extra-intestinal spread of bacterial infection.
- Younger than 6 months with salmonella gastroenteritis.
- With *Clostridium difficile*-associated pseudomembranous colitis, giardiasis, dysenteric shigellosis, dysenteric amoebiasis or cholera.
- Seek specialist advice about antibiotic therapy for children who have recently been abroad.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA): *DRUG SAFETY UPDATE* (JULY 2009)

Clopidogrel and proton pump inhibitors: interaction

The July issue of the Drug Safety Update provides more background information on the interaction between clopidogrel and PPIs:

- The active metabolite of clopidogrel is formed by the CYP2C19 isoenzyme and several studies including large outcome studies have previously shown that the effectiveness of clopidogrel is reduced if the activity of the CYP2C19 enzyme activity is reduced due to an underlying metabolic disorder.
- In-vitro studies conducted with all five PPIs have shown that to varying degrees they all competitively inhibit CYP2C19.
- Various cohort studies and a case control study have shown an attenuation of the clinical benefit of clopidogrel by concomitant PPI use in patients with previous coronary artery restenosis or acute MI with significant results as little as 90 days after starting therapy.
- The Clopidogrel Medico Outcomes Study of 16, 690 patients who were taking clopidogrel after stenting found that the event rate for a composite risk of admission to hospital for MI, stroke, unstable angina or repeat revascularisation was 18% for clopidogrel users without concomitant PPIs, 24% with lansoprazole, 25% with esomeprazole, 25% with omeprazole and 29% with esomeprazole. All event rates were statistically significant compared with the rate in users of clopidogrel alone.
- Another study found an increased risk of cardiovascular events in those taking clopidogrel with any PPI (odds ratio 1:4 [95% CI 1.1-1.8]) and no significant increase in those taking clopidogrel with pantoprazole (odds ratio 1:02 [95% CI 0.7-1.5]) However, the authors noted that the overlapping 95% CI suggest that the difference between the two groups was not significant.
- More evidence is required from clinical outcome studies before any specific recommendations can be made for the risk associated with individual PPIs.
- On the basis of pharmacokinetic data, other medicines for the treatment of gastrointestinal disorders such as H2 blockers or antacids would not be expected to interact with clopidogrel. However there are currently no substantial data from clinical-outcome studies to support this.

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 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. Concomitant use of a PPI and clopidogrel is not recommended unless considered essential.
(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.
(4) Ensure that patients prescribed clopidogrel are not self-medicating with over-the-counter omeprazole
PACEF will continue to keep this advice under review.

Long-acting ß agonists in chronic obstructive pulmonary disease

The MHRA have issued the following advice for healthcare professionals:

- The overall benefits of Long-acting ß agonists (LABAs) both as monotherapy and in combination with inhaled corticosteroids (ICS) in the treatment of chronic obstructive airways disease (COPD) continue to outweigh any risks.
- LABAs should be used in line with current GOLD and NICE guidelines.
- **ICS should not be used alone in the treatment of COPD and should only be introduced when there is severe disease.**
- A key issue is the increased risk of pneumonia with ICS treatment in COPD. The risk is not apparent with the use of LABA monotherapy.

Mycophenolate mofetil and pure red cell aplasia

- Up to April 2009 there have been reports of 41 cases of pure red cell aplasia associated with Mycophenolate mofetil (CellCept).

The MHRA have issued the following advice for healthcare professionals:

- Dose reduction or discontinuation of mycophenolate mofetil should be considered in patients who develop red cell aplasia. Changes to treatment should only be done under specialist supervision to minimise the risk of graft rejection.
-

PACEF Recommendation:
All prescribing of myclophenolate within primary care should be done within the framework of a shared care guideline It is the responsibility of the specialist service to provide advice to the GP if the biochemical values including blood results that are being monitored fall outside the normal range and for the specialist service to manage any dose alterations that are required as a result of this.

Clarification: ACE Inhibitors and angiotensin II receptor antagonists – use during breast feeding

The MHRA have clarified the following points:

- Although ACE inhibitors and angiotensin II receptors antagonists are generally not recommended for use by breastfeeding mothers they are not absolutely contraindicated.
- Healthcare professionals may prescribe these medicines during breastfeeding if they consider that this treatment is essential.
- In particular the original article advised that in mothers who are breastfeeding older infants, the use of captopril, enalapril or quinapril may be considered if an ACE inhibitor is necessary for the mother.
- Careful follow-up of the infant for possible signs of hypotension is recommended.

LEGAL ADVICE: PATIENT CONSENT TO CHANGES IN MEDICATION

Following a recent query from a practice, legal clarification has been sought on the requirement for patient consent prior to changes being made to medication. Specifically, this query arose in response to standard practice around the local implementation of therapeutic switch initiatives. Typically, following agreement from a practice to make a recommended change to prescribing, staff from the NHSL Prescribing and Medicines Management Team work in practice to identify

appropriate patients for the proposed switch and, subject to GP approval, notify patients of the intended switch by letter. Patients are identified according to set protocols and standard operating procedures (SOPs). If the GP approves the patient for the switch and the patient does not formally opt-out of the switch by raising concerns in response to the letter, the switch is implemented and the patient receives a prescription for the replacement therapy at their next repeat. The recent practice query was based on concern that no response to the letter from the patient was taken to signify consent; the practice preferred an approach which required the patient to formally respond to the letter in the affirmative, the so-called 'opt-in' approach.

In response to this, NHSL have obtained advice from Beachcroft Solicitors who have advised as follows:

- The NHS Act 2006 supports the patient's right to treatment, but not the patient's right to choice of intervention or choice of drug.
- The Department of Health supports therapeutic switch initiatives as long as quality is maintained and cost-effectiveness assured.
- Prior to any medical intervention or procedure, the patient must be appropriately informed of the risks and possible complications through dialogue, explanation and discussion. Patient consent following such information can be evidenced by the clinical record and, in the case of a medicine, the acceptance of the prescription by the patient.
- Once the patient has consented to treatment, the patient cannot dictate choice of treatment, although adverse drug reactions, cautions, contra-indications, interactions etc must be taken into account by the clinician.
- A properly considered therapeutic switch programme that utilizes an 'opt-out' approach (i.e. the patient is assumed to be participating unless they specifically notify the practice/GP that they do not wish to take part) is lawful.
- NHS Lincolnshire should standardize their approach to therapeutic switching to ensure that processes are robust and uniformly followed in all Lincolnshire practices using prescribing technician switch support.

PACEF Recommendation:
As a result of this, PACEF have recommended a standard approach to therapeutic switching which should be followed in all technician supported switches across Lincolnshire. The approved approach should ensure that all patients are fully informed of the switch in writing and given the opportunity to 'opt-out' prior to the issue of the first prescription for the new treatment if they wish. If the patient does not choose to intervene, the assumption should be made that they have consented to the switch by implication. All switches will be supported by Standard Operating Procedures (SOPs) and standard patient letters approved in advance by the Prescribing Operational Group acting as a formal Sub-Committee of PACEF. All new therapeutic switches must be approved by PACEF prior to advocacy to practices and technician implementation.

Acknowlegements
Many thanks to Cathy Johnson, Interface Lead Pharmacist, and Gill Kaylor, Prescribing Adviser, for their contributions to this edition of the *PACE Bulletin*.

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