NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 3; Number 13 **December 2009**

MERRY CHRISTMAS AND A HAPPY NEW YEAR TO ALL OUR READERS

What's new this month:

- **The use of low-dose aspirin for the primary prevention of cardiovascular disease is no longer recommended (see page 3).**
- **New generic clopidogrel salts have been evaluated and generic prescribing is advocated (see page 4).**
- **Qlaira, a new phasic combined oral contraceptive has been designated RED-RED (see page 5).**
- **The prescribing of fentanyl transdermal patches is reviewed and Matrifen patches are identified as the fentanyl patch of choice (see page 7).**
- **The use of antimuscarinics in the treatment of urge urinary incontinence, overactive bladder or mixed urinary incontinence is reviewed (see page).**
- **Practical guidance is given on the use of the swine flu vaccines, Pandemrix and Celvapan (see page 10).**
- **Prophylactic paracetamol at the time of vaccination may affect the antibody response (see page 12).**

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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: NOVEMBER 2009 UPDATE

Drug	Indication(s)	Traffic Light Status
Betamethasone valerate adhesive plaster (Betesil)	Steroid responsive dermatoses	RED-RED
Caphosol electrolyte solution	Dry mouth, particularly oral mucositis, hyposalivation or xerostomia.	RED ACBS.
Estradiol valerate/ dienogest combined oral contraceptive pill (Qlaira)	Oral contraception	RED-RED
Fentanyl transdermal reservoir patch (Fentalis)	Severe chronic pain	RED-RED
Fentanyl transdermal matrix patch (Matrifen)	Severe chronic pain	GREEN First line fentanyl patch of choice. Should be prescribed by brand to maximise cost-effectiveness
Influenza A (H1N1)v (swine flu) vaccine (Celvapan)	Influenza immunisation in accordance with official guidance in a pandemic	GREEN
Influenza A (H1N1)v (swine flu) vaccine (Pandemrix)	Influenza immunisation in accordance with official guidance in a pandemic	GREEN
Orciprenaline sulphate syrup 10mg in 5ml (Alupent)	Licensed for reversible airways obstruction	RED-RED
Prasugrel tablets 5mg and 10mg (Efient)	Licensed in combination with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI).	RED
Topotecan intravenous infusion (Hycamtin)	Licensed in combination with cisplatin for the treatment of recurrent carcinoma of the cervix, after radiotherapy, and for patients with stage IVB disease.	RED
Trospium chloride sustained release capsules 60mg (Regurin XL)	Urge incontinence, increased urinary frequency and urgency in patients with overactive bladder	GREEN Second line, for those unresponsive or intolerant to oxybutynin

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.**

ASPIRIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

Regular readers of the *PACE Bulletin* will have followed the unfolding debate around the role of aspirin in the primary prevention of cardiovascular disease (CVD). PACEF have now completed a wide ranging review of the subject including an assessment of the key trials and a careful consideration of the MHRA position and the recent *Drug and Therapeutics Bulletin* entitled 'Aspirin for primary prevention of cardiovascular disease?' Our conclusions are as follows:

- There are an increasing number of trials and meta-analyses that conclude that the benefits of prescribing low-dose aspirin for the primary prevention of CVD are partially or completely offset by the harms. **The Antithrombotic Trialists' Collaboration have estimated that around 2,000 people need to be treated for one year to prevent one non-fatal MI; similarly treating 3,300 people for a year will cause one major gastrointestinal or other extra-cranial bleed.**
- In addition, low-dose aspirin is only licensed for the prevention of thrombotic cerebrovascular or cardiovascular disease in those who already have vascular disease (secondary prevention); primary prevention is unlicensed.
- Currently available evidence does not justify the routine use of low-dose aspirin for the primary prevention of CVD in apparently healthy individuals, including those with elevated BP or diabetes.

PACEF Recommendations:
(1) All new initiations of low-dose aspirin for the primary prevention of CVD should cease.
(2) All patients currently taking aspirin for primary prevention (both prescribed and over the counter) should be reviewed at an appropriate time (i.e. at their next medication review); patients should be fully informed of the evidence of benefits and harms and encouraged, where possible, to stop.
(3) When considering the risks for each individual, prescribers should be mindful of the unlicensed status of aspirin in this context and the gastro-intestinal risk, particularly in those with risk factors for GI bleeding. Patients already experiencing dyspepsia (which may require symptomatic treatment) or at high gastrointestinal risk may experience more harm from aspirin than benefit.
(4) When considering the benefits, prescribers should be mindful that current evidence does not justify the routine use of low-dose aspirin for the primary prevention of CVD in apparently healthy individuals, including those with elevated BP or diabetes.
(5) Discontinuation of low-dose aspirin for primary prevention in patients already taking a range of other medicines will provide an excellent opportunity to simplify the patient's prescription.
(6) It must be emphasized that the use of low-dose aspirin in the secondary prevention of CVD has a substantial overall benefit and should not be affected by this guidance.

References:
MHRA, *Drug Safety Update* (October 2009)
DTB, Vol 47, No 11 (November 2009)

PRESCRIBING GENERIC CLOPIDOGREL

Prescribers will already be aware from *PACE Bulletin*, Vol 3 No 10 (October 2009) that a variety of generic clopidogrel products are now available 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. Most of the clopidogrel generics have been granted marketing authorisations by the European Medicines Agency (EMEA) as follows:

Indicated in adults for the prevention of atherothrombotic events in:

(1) Patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than six months) or established peripheral arterial disease.
(2) Patients suffering from acute coronary syndrome (ACS):
    - Non-ST segment elevation ACS (unstable angina or non-Q-wave MI), including patients undergoing a stent replacement following percutaneous coronary intervention, in combination with acetylsalicylic acid (ASA).
    - ST segment elevation acute MI, in combination with ASA in medically treated patients eligible for thrombolytic therapy.

All of the generic companies have successfully demonstrated bioequivalence to clopidogrel hydrogen sulphate (Plavix) in order to gain these marketing authorisations. However, in the UK, Sanofi Aventis hold a patent which precludes generic manufacturers from including combination use of clopidogrel with aspirin in ACS as a licensed indication in the product SPC..

It is acknowledged that the use of unlicensed medicines or off-label use of licensed medicines rests with the prescriber, who remains professionally accountable for their judgement and may be called upon to justify their actions. However, due to the demonstrated bioequivalence of the products and the existence of the EMEA marketing authorisations, the risk associated with off-label prescribing of generic clopidogrel is low. Prescribers will be aware of other generics (e.g. omeprazole) that do not carry all of the licensed indications of the originator molecule, but are nonetheless widely prescribed interchangeably.

From December 1st 2009, clopidogrel 75mg tablets moved to category A of Part VIII of the *Drug Tariff*. This means that the reference price for clopidogrel is now calculated as the average of prices listed by: AAH, Alliance Healthcare, Teva and Activas. As a result of this, the reimbursement price is already beginning to fall. Contractors will be reimbursed at this price for all scripts for clopidogrel tablets 75mg, clopidogrel besilate tablets 75mg, and clopidogrel hydrochloride tablets 75mg; scripts for clopidogrel hydrogen sulphate tabs 75mg will be reimbursed at the Plavix price subject to endorsement. Future movement of generic clopidogrel into Category M could create a significant gap between the generic price and the originator brand price which could equate to substantial future savings across the county in excess of £1M pa.

PACEF Recommendations:
(1) Clopidogrel generics hold the appropriate EMEA marketing authorisations, have demonstrated their bioequivalence to clopidogrel hydrogen sulphate (Plavix), but are unable to list combination use with aspirin in ACS among their licensed indications due to the originator brand manufacturer holding a patent for this indication. Although combination use of generic clopidogrel and aspirin in ACS is technically off-label, PACEF have judged this to be low risk and would encourage all prescribers to prescribe clopidogrel generically in future.
(2) In order to maximise cost-effectiveness, prescribers are asked 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.

NEW DRUG ASSESSMENT: ESTRADIOL VALERATE/ DIENOGEST COMBINED ORAL CONTRACEPTIVE PILL (QLAIRA)

Qlaira is a multiphasic combined oral contraceptive (COC) containing estradiol valerate and dienogest. The product has a complex quadraphasic dosage regimen designed to optimise cycle control. The contents and order of the pills in each pack are as follows:

Number of pills	Colour	Estradiol valerate (mg)	Dienogest (mg)
2	Dark yellow	3	0
5	Medium red	2	2
17	Light yellow	2	3
2	Dark red	1	0
2	White	0	0

Qlaira is the first COC to utilise the natural estrogen, estradiol valerate, which is metabolised in the body to estradiol, a natural human estrogen. PACEF reviewed two Phase 3 clinical trials which demonstrate the effectiveness of Qlaira as a method of contraception in comparison to other combined pills and suggest better cycle control in terms of shorter lighter withdrawal bleeds and fewer episodes of breakthrough bleeding. However, the comparator pill used in the study claiming better cycle control was Miranova, a lower estrogen COC (containing 20microgram of ethinylestradiol) not currently available in the UK.

In comparison with other COCs, Qlaira is significantly more expensive:

Combined Oral Contraceptive	**Pack**	**Cost (£) 28 days**
Qlaira	**3 x 28 tabs**	**£8.39**
Yasmin	3 x 21 tabs	£4.90
Marvelon	3 x 21tabs	£2.19
Cilest	3 x 21 tabs	£0.99
Logynon	3 x 21 tabs	£1.32
Microgynon 30	3 x 21 tabs	£0.96
Loestrin 20	3 x 21 tabs	£0.92
Ovysmen	3 x 21 tabs	£0.51

PACEF Recommendation:
A number of concerns arise from scrutiny of the trial data. Only one of the trials reviewed has been published in full; one was only available in abstract. The single trial substantiating claims of better cycle control used an unfamiliar comparator (Miranova) which contains a lower dose of ethinylestradiol (20mcg) than that found in UK alternatives such as Microgynon 30. Whether Qlaira would perform as well or better in terms of cycle control than this widely prescribed first-line alternative remains to be seen. In addition, while the concept of a more natural pill may appeal to some women, the evidence for clinically significant benefits over COCs containing synthetic estrogen is lacking. Finally, the quadraphasic dosage regimen is complex and prone to error and the price is substantially higher than even the most expensive alternative. As a result of all these factors, Qlaira is designated RED-RED.

NEW DRUG ASSESSMENT: CAPHOSOL SOLUTION

Caphosol is a supersaturated calcium phosphate rinse used for oral mucositis, hyposalivation or xerostomia. It is classified as a class one medical device rather than a licensed medicine. Caphosol is supplied as two single-dose containers, one containing a phosphate solution (15ml) and the other a calcium solution (15ml) which, when combined in equal volumes, form a solution supersaturated with both calcium and phosphate ions. A small scale randomised controlled trial in patients undergoing haematopoietic stem cell transplantation demonstrated superior performance to fluoride rinsing in terms of fewer days of mucositis, shorter duration of pain and less use and shorter duration of opiate analgesia. Potential alternatives, such as oxetacaine and antacid (unlicensed) and saliva replacement products are lower cost, but not always effective. Scrutiny of the supply chain revealed some evidence of product shortage and distribution problems, particularly in primary care.

PACEF Recommendation;
PACEF were convinced of a small scale role for this product in a limited range of patients. Due to potential supply problems in primary care it was decided to designate the product RED. It should be initiated by a specialist and supplied totally from within ULHT; any approaches to GPs to prescribe should be refused.

RAPID DRUG ASSESSMENT: BETAMETHASONE ADHESIVE PLASTER (BETESIL)

Betamethasone valerate adhesive plaster (Betesil) is licensed for the treatment of a range of inflammatory skin disorders, although it is being specifically promoted as a treatment for chronic plaque psoriasis affecting the knees, elbows and shins. Local guidance does not recommend use of high potency corticosteroids for the management of psoriasis due to the risk of flare following discontinuation. Potent steroids, such as betamethasone valerate, are usually reserved for cases that do not respond to moderately potent steroids. Haelan tape, containing the moderately potent steroid fludroxycortide, has recently been approved for use by ULHT dermatologists for the treatment of chronic recalcitrant dermatoses. Direct cost comparisons between alternative steroid formulations and Betesil reveal that on average a month's treatment will cost approximately £70 more per patient with Betesil than with conventional high potency topical steroids.

Local dermatologist advice is that there is no proven clinical advantage to the use of Betesil adhesive plaster over Haelan tape.

PACEF Recommendation:
In view of the lack of convincing evidence and the expensive nature of the product, betamethasone adhesive plaster (Betesil) is designated RED-RED.

RAPID DRUG ASSESSMENT: FENTANYL TRANSDERMAL RESERVOIR PATCH (FENTALIS)

Fentalis is a new fentanyl transdermal reservoir patch licensed for the treatment of severe chronic pain. Most of the more recently marketed transdermal fentanyl patches have tended to be matrix style formulations. Reservoir patches consist of a dose of fentanyl contained within an alcoholic gel; in the matrix formulation fentanyl is dissolved evenly in each layer. Matrix patches are generally smaller and thinner than their equivalent reservoir patch. There is no evidence of a difference in the rate of delivery between different brands of the same strength when used in accordance with their product licence. Reservoir and matrix patches are bioequivalent and patients can be switched from one to the other without loss of efficacy or increase in undesirable effects, although, as with any analgesic, patient allegiance to a particular formulation can quickly develop. Reservoir patches must not be cut as damage to the rate limiting membrane can lead to a rapid release of fentanyl that can result in the patient receiving an overdose. In the event that the patch needs to be cut, a matrix style patch must be used. Prescribers are reminded that cutting the patch renders it an unlicensed medicinal product and that this practice is not recommended by the MHRA.

A cost comparison of the different fentanyl patches currently available reveals the following:

Fentanyl transdermal patch	Dose mcg/hr	Cost (5 patches)
Fentalis (reservoir)	**25**	**£26.94**
	50	**£50.32**
	75	**£70.15**
	100	**£86.46**
Durogesic DTrans (matrix)	12	£18.11
	25	£25.89
	50	£48.36
	75	£67.41
	100	£83.09
Matrifen (matrix)	12	£13.78
	25	£19.69
	50	£36.78
	75	£51.27
	100	£63.20
Mezolar Matrix (matrix)	12	£13.75
	25	£19.65
	50	£36.75
	75	£51.25
	100	£63.15

PACEF Recommendation:
Local and national guidance emphasizes the bioequivalence of reservoir and matrix fentanyl patches between different brands of the same strength when used in accordance with their product licence. Matrix style patches are increasingly preferred because they are smaller and thinner. In comparison to currently available matrix patches, Fentalis patches emerge as more expensive with a slightly narrower range of strengths. As a result of this, PACEF could see no advantage in the Fentalis transdermal reservoir patch and it was designated: RED-RED. Closer scrutiny of the comparative costs of the matrix patches reveals a significant cost advantage in standardising fentanyl patch prescribing around the Matrifen brand wherever possible. Generic prescribing of fentanyl patches is still reimbursed against the Durogesic DTrans price in primary care. Prescribers are advised to ensure that new initiations of fentanyl patches should be for the Matrifen brand. Existing patients receiving fentanyl patches as part of their end-of-life care should be maintained on their current brand and not switched. Patients with stable chronic pain requiring a fentanyl patch should be standardised on Matrifen; product switching should be considered for this indication as a way of maximising cost-effectiveness. Analysis of Lincolnshire prescribing data reveals that the majority of fentanyl patches are currently prescribed generically. Open generic scripts for fentanyl patches are generally filled with the branded product that the patient has previously used. Branded prescribing of Matrifen transdermal patches is advocated where possible.

RAPID DRUG ASSESSMENT: TROSPIUM CHLORIDE SUSTAINED RELEASE CAPSULES 60MG (REGURIN XL)

A new once daily modified-release formulation of trospium chloride has been launched under the brand name of Regurin XL; it is licensed for urge incontinence, increased urinary frequency and urgency in patients with overactive bladder.

The safety, efficacy and tolerability of MR trospium has been evaluated in two randomized, double-blind, placebo-controlled trials. Compared with placebo, trospium MR 60mg once daily for 12 weeks resulted in significant improvements in overactive bladder symptoms (frequency, urinary incontinence and urgency).
A UKMI Therapeutic Class Summary in 2008 suggested that there is little difference in efficacy between antimuscarinic drugs for overactive bladder syndrome in adults; approximately 56% of patients will experience an improvement in symptoms, regardless of which antimuscarinic is used. Similarly, NICE Clinical Guideline 40, *Urinary incontinence: the management of urinary incontinence in women* (October 2006), states that for urge urinary incontinence (UI)/ overactive bladder (OAB) or mixed UI (where urge is the dominant symptom):

- First line treatment should be **bladder training** lasting for a minimum of 6 weeks.
- If bladder training is ineffective or if frequency remains troublesome, antimuscarinic drugs will need to be considered. Immediate release non-proprietary **oxybutynin** should be offered as a first choice. The patient will need to be made aware of the potential adverse effects of antimuscarinic drugs (e.g. dry mouth, blurred vision, abdominal discomfort, drowsiness, nausea and dizziness).

- There is no evidence of a clinically important difference in efficacy between the various antimuscarinic drugs, although failure to tolerate immediate release (IR) oxybutynin may necessitate a trial of an alternative agent. Oxybutynin extended release (Lyrinel XL) should be considered as a second line alternative in patients responsive to oxybutynin, but intolerant to the IR formulation. Other alternatives include: **solifenacin (Vesicare)**, **tolterodine (Detrusitol/Detrusitol XL)**, **trospium (Regurin)** or **transdermal oxybutynin (Kentara)**.

A cost comparison of the alternative therapies reveals the following:

	Dose	**28 Day Cost**
Oxybutynin tablets 2.5mg (generic)	**2.5mg twice daily**	**£7.36**
Oxybutynin tablets 3mg (Cystrin)	**3mg twice daily**	**£9.15**
Oxybutynin tablets 5mg (generic)	**5mg twice daily**	**£5.89**
Oxybutynin tablets 5mg (generic)	**5mg three times daily**	**£12.82**
Oxybutynin MR tablets 5mg (Lyrinel XL)	5mg daily	£10.30
Oxybutynin MR tablets 10mg (Lyrinel XL)	10mg daily	£20.58
Oxybutynin MR tablets 10mg (Lyrinel XL)	20mg daily	£41.16
Oxybutynin transdermal patch 3.9mg per 24 hours (Kentara)	1 patch twice weekly	£27.20
Solifenacin tablets 5mg (Vesicare)	5mg once daily	£25.78
Solifenacin tablets 10mg (Vesicare)	10mg once daily	£33.51
Tolterodine tablets 2mg (Detrusitol)	2mg twice daily	£30.56
Tolterodine SR tablets 4mg (Detrusitol XL)	4mg once daily	£25.78
Trospium chloride tablets 20mg (Regurin)	20mg twice daily	£24.27
Trospium chloride sustained release capsules 60mg (Regurin XL)	60mg once daily	£23.05
Propiverine tablets 15mg (Detrunorm)	15mg twice daily	£24.45
Propiverine MR capsules 30mg (Detrunorm XL)	30mg once daily	£24.45
Duloxetine capsules 20mg (Yentreve)	20mg twice daily	£36.96
Duloxetine capsules 40mg (Yentreve)	40mg twice daily	£36.96

All prices are compiled from *MIMS* December 2009 or the *Drug Tariff* December 2009.

PACEF Recommendation:
Immediate release oxybutynin tablets remain the first-line choice for urge urinary incontinence, overactive bladder or mixed UI. For patients responsive to oxybutynin, but intolerant to the immediate release formulation, modified release oxybutynin tablets (Lyrinel XL) should be considered. Solifenacin (Vesicare), **tolterodine (Detrusitol/Detrusitol XL)**, **trospium (Regurin/Regurin XL)** or **transdermal oxybutynin (Kentara) are all endorsed by NICE as possible second line alternatives**. **Trospium chloride sustained release capsules 60mg (Regurin XL) have been evaluated by PACEF and approved for use. Designation: GREEN. Cost comparison to alternative agents approved by NICE reveals that Regurin XL is lower cost than most alternatives and should be considered preferentially.**

RAPID DRUG ASSESSMENTS: INFLUENZA A (H1N1)V SWINE FLU VACCINES (PANDEMRIX AND CELVAPAN)

Two new Influenza A (H1N1)v vaccines have been licensed for use in the UK: Pandemrix (manufactured by GlaxoSmithKline) and Celvapan (manufactured by Baxter Healthcare). Key points relating to the products and vaccination programme are as follows:

- Pandemrix is a split virion, inactivated, adjuvanted vaccine.
- Celvapan is a whole virion, inactivated, vero cell derived vaccine.
- Both of the vaccines are inactivated, do not contain live viruses and cannot cause flu.
- Pandemrix is supplied in multi-dose vials. It must be used within 24 hours after mixing, stored either in a fridge or at room temperature.
- Celvapan must be used within three hours once the vial has been removed from the fridge (even if the bung has not been pierced).
- Both vaccines should be stored at 2 to 8^0C.
- Pandemrix requires reconstitution before use. Clear instructions are given in the 'Green Book' section entitled *Pandemic influenza: A(H1N1) v 2009 (swine flu)*. All of the adjuvant emulsion should be drawn up and injected into the vial containing the antigen suspension. This will create a mixed vial containing ten 0.5ml doses. There is a deliberate overage built in to ensure that ten doses can be administered from the mixed vial.
- Celvapan is supplied already mixed in a multi-dose vial. Each vial contains ten 0.5ml doses.
- The two vaccines are not interchangeable; the same vaccine must be used if a two-dose schedule is being followed.
- Children aged 6 months to 18 years should receive Pandemrix (if available) as there are currently no data on the use of Celvapan in children.
- The recommended dosage schedules are as follows:

	Age	Dose
Pandemrix	Children aged 6 months to under 10 years	A single injection of 0.25ml (i.e. half the normal dose) unless the child is immunosuppressed or has an immune deficiency.
Pandemrix	Immunocompromised children aged 6 months to under 10 years	Two doses of 0.25ml given at least three weeks apart
Pandemrix	Adults and children aged	A single injection of 0.5ml

	10 years and above	
Pandemrix	Immunocompromised individuals aged 10 years and above	Two doses of 0.5ml given at least three weeks apart
Pandemrix	Pregnant women	A single injection of 0.5ml
Celvapan	Adults and children aged 6 months and above	Two doses of 0.5ml given at least three weeks apart

- A (H1N1)v vaccine can be given at the same time as other vaccines including seasonal influenza vaccine and other childhood vaccines. Vaccines should be given at separate sites, preferably in different limbs.
- Individuals who have had influenza A(H1N1)v infection can safely be vaccinated, although vaccination provides no additional benefit for those who have had laboratory confirmed infection. In the absence of a documented laboratory confirmed diagnosis, individuals should be vaccinated.
- Certain groups of people are at higher risk of developing complications from influenza A(H1N1)v. This clinical at-risk groups are defined in detail in the 'Green Book' (Chapter 23a) and include those with chronic respiratory disease, asthma, chronic heart disease, chronic renal disease, chronic liver disease, chronic neurological disease, diabetes requiring insulin or oral hypoglycaemic drugs and immunosuppression due to disease or treatment. Pregnant women are also included.
- A higher proportion of the over-65s appear to have some immunity to A(H1N1) as a result of exposure to similar viruses in the past. As a result, healthy individuals over 65 are not being prioritised for this vaccination.
- Immunocompromised individuals may have a sub-optimal immunological response to the vaccine and require two doses at least 3 weeks apart. Household contacts of these patients should be offered vaccination to reduce the risk of exposure.
- Front line health and social care workers are being prioritised for vaccination. Frontline staff are those who have regular clinical contact with patients and who are directly involved in patient care.
- All pregnant women should be vaccinated as they are at increased risk of complications of swine flu. Pandemrix is the recommended vaccine in this group as it gives adequate levels of antibodies after a single dose giving more rapid protection than Celvapan.
- Prophylaxis after contact with a case of pandemic flu needs to be considered in those at highest risk (see above). Prophylaxis with antivirals should be considered regardless of vaccination status, particularly in the immunocompromised who may have a sub-optimal response to vaccine.
- The swine flu vaccination programme has now been extended to include children between the ages of six months and five years.

PACEF Recommendation:
Both vaccines have been approved for use within the NHS by the Dept of Health and the Joint Committee on Vaccination and Immunisation and are already available. Both are designated GREEN by PACEF.

NEW TRIALS IN BRIEF

Prophylactic paracetamol at the time of vaccination may affect antibody response

Two open-label RCTs in 459 infants in the Czech republic randomly assigned patients to receive 3 prophylactic doses of paracetamol or no doses in the 24h post vaccination period following DTPa-HBV-IPV-Hib, oral rotavirus vaccine and a 10 valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (primary dose or booster dose). Prophylactic paracetamol significantly reduced the incidence of a raised temperature (the primary outcome); fever was uncommon in both groups. However, antibody responses to several vaccine antigens (geometric mean concentrations) were significantly lower in the prophylactic group.

PACEF Recommendation:
These studies suggest that prophylactic paracetamol post-vaccination may compromise antibody response to some vaccines. Paracetamol oral suspension as necessary to treat raised temperature post-vaccination remains preferred practice.

Reference: Prymula R et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in two open-label, randomised controlled trials. *The Lancet* 2009; 374:1339-1350.

ACE Inhibitors and Angiotensin Receptor Blockers in patients with ischaemic heart disease

A systematic review of RCTs of at least 6 months' duration comparing ACE inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs) or combination therapy with placebo or active control in patients with ischaemic heart disease and preserved ventricular function. Moderate to high strength evidence (7 trials, n=32,559) showed that ACEIs reduce the relative risk for total mortality and non-fatal MI compared with placebo. Low strength evidence (1 trial, n=5926) suggested that ARBs reduce the relative risk for a composite end point of CV mortality, non-fatal MI or stroke, but not for the individual components. Moderate strength evidence (1 trial, n= 25 620) showed similar effects on total mortality and MI, but an increased risk for discontinuations because of hypotension and syncope with combination therapy compared with ACE inhibitors alone.

PACEF Comment:
This systematic review reinforces the first line position of ACEIs within this context on the basis of both best evidence and cost-effectiveness. The increased risk of hypotension and syncope with ACEI/ARB combination therapy is also emphasized. A more detailed review of this area will be undertaken by PACEF in early 2010.

Reference: Baker WL et al. Systematic Review: Comparative effectiveness of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers for ischaemic heart disease. *Ann Intern Med* 15 December 2009; 151(12). Published early online 20 October 2009.

Antidepressant prescribing continues to rise

A detailed analysis of the UK general practice research database for 170 practices from 1993–2005 revealed that antidepressant prescribing nearly doubled (average number of prescriptions issued per patient rose from 2.8 in 1993 to 5.6 in 2004), while overall the incidence of new cases of depression and the proportion of patients

with depression treated with antidepressants in the first year of diagnosis remained stable. The increase in antidepressant prescribing is mainly explained by small changes in the proportion of patients receiving long term treatment.

PACEF Comment:
This analysis suggests that increased prescribing of antidepressants is not about more patients receiving antidepressants, but about patients being treated more appropriately with longer treatment courses. PACEF are in the process of reviewing new NICE Clinical Guidelines on the treatment and management of depression in adults and will be producing updated advice in early 2010.

Reference: Moore M et al. Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database. *BMJ* 2009; 339:b3999.

NICE TECHNOLOGY APPRAISAL 182: *PRASUGREL FOR THE TREATMENT OF ACUTE CORONARY SYNDROMES WITH PERCUTANEOUS CORONARY INTERVENTION* (OCTOBER 2009)

The key recommendations are as follows:

Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention only when:

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary or
- stent thrombosis has occurred during clopidogrel treatment or the patient has diabetes mellitus.

NICE evaluated the same RCT that was evaluated by PACEF in September 2009, the TRITON-TIMI 38 study. TRITON-TIMI 38 shows some advantages with prasugrel in terms of effectiveness, including statistically significant reductions in a composite endpoint, non-fatal MI and stent thrombosis compared to clopidogrel. In terms of safety, an increased rate of major bleeds (including fatal bleeds) occurred with prasugrel compared with clopidogrel. Overall, all-cause mortality, CV death and non-fatal stroke did not differ significantly between groups. NICE conclude that prasugrel and clopidogrel are broadly equivalent in terms of clinical effectiveness at 15 months for patients with ACS having PCI.

In terms of cost-effectiveness, they conclude that prasugrel is only cost-effective in the sub-groups identified. They are aware of the cost differential between the two drugs and the likelihood of a widening gap as the clopidogrel price begins to fall. At present, the comparative costs are as follows:

Drug	Daily dose	28 day cost
Prasugrel 5mg tablets (Efient)	5mg daily	£47.56
Prasugrel 10mg tablets (Efient	10mg daily	£47.56
Clopidogrel 75mg tablets (Plavix)	75mg daily	£33.93
Clopidogrel 75mg tablets (generic)	75mg daily	£31.50

NICE acknowledge that the SPC for prasugrel states that combination use with proton pump inhibitors is possible as the antiplatelet activity of prasugrel is not significantly affected by specific PPIs. However, they urge caution as this interaction

has not been extensively studied. At present, prasugrel cannot be seen as an alternative to clopidogrel where a PPI is indicated.

PACEF Recommendation:
In view of these NICE recommendations, prasugrel is re-classified as RED. At present, the main interest in prasugrel is from cardiologists in tertiary centres. There are plans to develop shared care guidelines in the future. As a result of this, prasugrel will be kept under review.

NICE TECHNOLOGY APPRAISAL 183: *TOPOTECAN FOR THE TREATMENT OF RECURRENT AND STAGE IVB CERVICAL CANCER* (OCTOBER 2009)

The key recommendation is as follows:

- Topotecan in combination with cisplatin is recommended as a treatment option for women with recurrent or stage IVB cervical cancer only if they have not previously received cisplatin.

PACEF Recommendation:
Topotecan injection (Hycamtin) is designated RED in combination with cisplatin for the treatment of recurrent carcinoma of the cervix, after radiotherapy, and for patients with stage IVB disease.

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

Bisphosphonates and osteonecrosis of the jaw

- The risk of osteonecrosis of the jaw (ONJ) is greater for patients receiving IV bisphosphonates for cancer than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease.
- All patients with cancer should have a dental check-up before bisphosphonate treatment. **All other patients who start bisphosphonates should have a dental examination only if they have poor dental status.**
- **During bisphosphonate treatment, patients should be encouraged to: maintain good oral hygiene; receive routine dental check-ups; and report any oral symptoms such as dental mobility, pain or swelling.**
- **The risk of developing ONJ in association with oral bisphosphonates seems to be low.**
- There is clear evidence to suggest bisphosphonate-specific and indication-specific risk factors such as potency (highest for zoledronate); route of administration (e.g. IV ibandronate, pamidronate and zoledronate) and cumulative dose. The evidence base is less robust for other proposed risk factors (e.g. duration and type of malignant disease, concomitant treatment, smoking and comorbid conditions). However, healthcare professionals should consider these risk factors when evaluating an individual's risk of developing ONJ.
- **A history of dental disease – including invasive dental procedures, dental trauma, periodontal disease and poorly fitting dentures – is associated with an increased risk of ONJ.**

PACEF Recommendation:
The risk of ONJ with oral bisphosphonates is low. Nonetheless, patients taking bisphosphonates should be encouraged to maintain good oral hygiene, have

routine dental check-ups and report any oral symptoms such as dental mobility, pain or swelling. All patients with cancer should have a dental check-up before starting bisphosphonate treatment. All other patients who start bisphosphonates should have a dental examination only if they have poor dental status.

Vigabatrin for infantile spasms: risk of movement disorders and MRI abnormalities

- Cases of abnormal brain MRI findings have been reported, in particular in young infants treated for infantile spasms with high doses (>125mg/kg/day) of vigabatrin.
- Movement disorders including dystonia, dyskinesia and hypertonia have been reported in patients treated for infantile spasms. The balance of benefits and risks of vigabatrin should be evaluated on an individual patient basis. If new movement disorders occur during treatment with vigabatrin, consideration should be given to dose reduction or a gradual discontinuation of treatment in consultation with specialist advice.

Orciprenaline sulphate (Alupent): withdrawal due to unfavourable benefit-risk profile

- Orciprenaline sulphate is to be withdrawn from the UK market over the next year because a review has determined that the benefit-risk profile is unfavourable. Specifically, orciprenaline is associated with a significantly increased incidence of cardiac side effects, mainly palpitations and tachycardia.
- Patients who require a liquid oral formulation of a beta-agonist should be switched to a more selective short-acting beta2-agonist such as salbutamol or terbutaline.

PACEF Recommendation:
Following MHRA advice, orciprenaline sulphate syrup 10mg in 5ml (Alupent) is designated RED-RED.

Statins: updated product information in patient leaflets on adverse reactions

- Patients should be made aware that treatment with any statin may be associated with depression, sleep disturbances, memory loss and sexual dysfunction.
- Statins may very rarely be associated with interstitial lung disease.

Acknowlegements

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

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