NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 6; Number 2 **January 2012**

HAPPY NEW YEAR TO ALL OUR READERS

What's new this month?

- **A new low cost fentanyl transdermal patch (Fencino) has been approved for use; designation GREEN (see page 2).**
- **Naproxen/esomeprazole 500mg/20mg tablets (Vimovo) have been re-assessed and confirmed as RED-RED (see page 5).**
- **Risperidone long acting injection (Risperdal Consta) is designated AMBER for the maintenance treatment of schizophrenia; a shared care guideline is in development (see page 6).**
- **Following the publication of NICE TA 231, agomelatine (Valdoxan) for major depressive disorder is confirmed as RED; this drug should not be prescribed in primary care, but may continue to be used within LPFT (see page 7).**
- **Writing to patients on long-term benzodiazepines or z drugs to highlight the risks can help patients to reduce or stop their therapy (see page 8).**
- **The dronedarone shared care guideline has been updated to include the most recent safety concerns (see page 9).**
- **The MHRA have reviewed the safety of citalopram and escitalopram and have issued guidance (see page 10).**
- **The MHRA have reviewed safety concerns over calcium and vitamin D and have concluded that there is no convincing evidence of a link between calcium and vitamin D and cardiovascular events. Updated guidance on supplementation and product selection is provided (see page 13).**

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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.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: NOVEMBER 2011 UPDATE

Drug	Indication(s)	Traffic Light Status
Agomelatine 25mg tablets (Valdoxan)	Licensed for the treatment of major depressive episodes in adults.	RED
Azithromycin 15mg/g eye drops (Azyter)	Licensed for the topical treatment of purulent conjunctivitis and trachomatous conjunctivitis in both adults and children (over 2 years).	RED-RED
Fentanyl patches (Fencino)	Licensed for the treatment of severe chronic pain.	GREEN
Ketoprofen 100mg/omeprazole 20mg (Axorid) tablets	Licensed for the symptomatic treatment of osteoarthritis (OA), rheumatoid arthritis and ankylosing spondylitis in patients with a history or risk of NSAID associated GI erosion.	RED-RED
Mifamurtide (Mepact) intravenous infusion	Licensed for high-grade, resectable, non-metastatic osteosarcoma after complete surgical resection in patients 2 to 30 years of age at initial diagnosis.	RED
Naproxen 500mg/esomeprazole 20mg tablets (Vimovo)	Licensed for the symptomatic treatment of osteoarthritis (OA), rheumatoid arthritis and ankylosing spondylitis in patients at risk of NSAID associated gastric and or duodenal ulcers in whom lower doses of naproxen or other NSAIDs are not sufficient.	RED-RED
Retigabine tablets (Trobalt)	Licensed for the adjunctive treatment of focal seizures with or without secondary generalisation.	AMBER No shared care guideline required
Risperidone long acting injection (Risperdal Consta) 25mg, 37.5mg. 50mg	Licensed for the maintenance treatment of schizophrenia in patients stabilised with oral antipsychotics.	AMBER Shared care guidelines are in development

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.**

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: *FENTANYL PATCHES (FENCINO)*

Fencino is a newly launched low cost, matrix-style, transdermal fentanyl 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 rather than reservoir patches. The advantage of the matrix style patch is that the active drug is

dissolved evenly in each layer rather than being held in a single reservoir with drug delivery controlled by a rate limiting membrane. 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. Identical strengths of fentanyl patches (whether reservoir or matrix) are considered 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.

Other matrix-style patches, already available on the UK market include: Durogesic DTrans, Matrifen, Mezolar Matrix, Osmanil and Victanyl. A cost comparison reveals that Fencino and Matrifen patches are currently the lowest cost formulations (highlighted in bold):

Fentanyl transdermal patch (matrix/reservoir)	**Strength**	**Cost (£)**
	mcg/hr	**5 patches**
Fencino (matrix)	**12mcg**	**£8.88**
	25mcg	**£12.69**
	50mcg	**£23.70**
	75mcg	**£33.04**
	100mcg	**£40.72**
Durogesic DTrans (matrix)	12mcg	£12.59
	25mcg	£17.99
	50mcg	£33.66
	75mcg	£46.99
	100mcg	£57.86
Fentalis (reservoir)	25mcg	£26.94
	50mcg	£50.32
	75mcg	£70.15
	100mcg	£86.46
Matrifen (matrix)	**12mcg**	**£8.87**
	25mcg	**£12.68**
	50mcg	**£23.69**
	75mcg	**£33.03**
	100mcg	**£40.71**
Mezolar Matrix (matrix)	12mcg	£13.75
	25mcg	£19.65
	50mcg	£36.75
	75mcg	£51.25
	100mcg	£63.15
Osmanil (matrix)	12mcg	£18.11
	25mcg	£26.94
	50mcg	£50.32
	75mcg	£70.15
	100mcg	£86.46
Victanyl (matrix)	25mcg	£15.94
	50mcg	£32.94
	75mcg	£38.94
	100mcg	£56.94

PACEF Recommendations:

Analysis of Lincolnshire prescribing trends has revealed that 66.7% of all prescriptions for fentanyl patches are still written generically. As fentanyl patches are classed as category C in the *Drug Tariff*, all generic prescribing is reimbursed at the price of the originator brand, Durogesic DTrans. In order to ensure continuity of supply for the patient and to maximise potential savings linked to specific named brands, prescribers are advised to prescribe fentanyl patches by brand name. Scrutiny of the cost comparison above reveals three broad price bands: (1) Lowest cost – Fencino, Matrifen; (2) Mid-range – Durogesic DTrans, Mezolar Matrix; (3) Highest cost – Fentalis, Osmanil and Victanyl. PACEF are mindful of the instability of the marketplace with regard to

these products, with recent price reductions rendering Matrifen comparable in price to Fencino. PACEF also recognise that many Lincolnshire practices have already undertaken work to standardise their prescribing around Matrifen, one of the two lowest cost brands and the product preferred by United Lincolnshire Hospitals. Taking these factors into account, Fencino fentanyl patches are designated GREEN and approved for use. Prescribers are asked to standardise their prescribing around one of the lowest cost products (Fencino or Matrifen). All prescribing of fentanyl patches should be by brand name. Highest cost fentanyl patches (Fentalis, Osmanil and Victanyl) should not be prescribed. Practices and CCGs wishing to minimise prescribing costs around transdermal fentanyl should consider switches to Fencino or Matrifen in practices that have yet to undertake the Matrifen switch. However, the instability of the trandermal fentanyl marketplace may render such initiatives unnecessary if mid-range products fall further in price.

RAPID DRUG ASSESSMENT: *AZITHROMYCIN EYE DROPS (AZYTER)*

Azithromycin 15mg/g eye drops (Azyter) constitutes the first macrolide based eye preparation and is licensed for the topical treatment of purulent conjunctivitis and trachomatous conjunctivitis in both adults and children (over 2 years). Clinical evidence in support of this product derives from two trials, one comparing azithromycin eye drops with oral azithromycin in children with trachomatous conjunctivitis and one comparing azithromycin eye drops and tobramicin 0.3% eye drops in a mixture of adult and paediatric patients with purulent conjunctivitis. Both trials showed non-inferiority to the active comparator. However, no comparative data exists to provide a meaningful comparison between azithromycin eye drops and more established first and second line treatments for conjunctivitis. Current local and national guidance recommends that if treatment of bacterial conjunctivitis is indicated, chloramphenicol 0.5% eye drops should be used first-line and fusidic acid 1% eye drops second line. Other broad spectrum antibacterials such as ciprofloxacin, ofloxacin or gentamicin are recommended third-line depending on microbial sensitivities and previous intolerance or contraindications to first-line agents.

A cost comparison between azithromycin eye drops and other alternatives reveals the following:

Drug	**Daily dose range**	**Cost (£) per bottle**
Azithromycin 15mg/g	**1 drop twice daily for 3 days**	**£6.99 (6 x single doses)**
Chloramphenicol 0.5% eye drops	1-2 drops up to 6 times daily or more frequently if required.	£1.53 (10ml)
Fusidic acid 1% eye drops	1 drop twice daily.	£2.00 (5g)
Ciprofloxacin 0.3% eye drops	1 -2 drops four times a day. In severe infections 1 drop every 2 hours for first 2 days then reduce to four times daily.	£4.70 (5ml)
Gentamicin 0.3% drops	1-2 drops up to 6 times daily. Severe infections initially 1-2 drops every 15-20 minutes reducing frequency once infection is controlled.	£2.13 (10ml)

PACEF Recommendation:
In the absence of any comparative data against a meaningful comparator, PACEF found it difficult to establish a role for azithromycin 15mg/g eye drops. In addition, this product is significantly more costly than even third line alternatives. As a result of this, azithromycin 15mg/g eye drops are designated RED-RED.

REVIEW: *NAPROXEN/ ESOMEPRAZOLE 500MG/20MG TABLETS (VIMOVO)*

Vimovo is a fixed dose combination of the non steroidal anti-inflammatory drug (NSAID) naproxen plus the proton pump inhibitor (PPI) esomeprazole. It is licensed for the symptomatic treatment of osteoarthritis (OA), rheumatoid arthritis and ankylosing spondylitis in patients at risk of NSAID associated gastric and or duodenal ulcers in whom lower doses of naproxen or other NSAIDs are not sufficient. According to NICE Clinical Guideline 59: *Osteoarthritis – the care and management of osteoarthritis in adults* (February 2008), oral NSAID/Cox-2 inhibitor therapy should be **co-prescribed with a PPI,** choosing the one with the lowest acquisition cost. Only two randomised controlled trials involving Vimovo have been published since PACEFs first assessment (see PACE Bulletin Vol 5 No 5 (March 2011). Both trials compare Vimovo one tablet twice daily with naproxen EC 500mg twice daily. Rather unsurprisingly, the lack of gastro-protection in the naproxen EC arm of both studies resulted in the incidence of gastric and duodenal ulcers in the naproxen EC arms being significantly higher than in the Vimovo arms.

PACEF Recommendation:
PACEF did not consider this to be sufficient evidence to change the existing classification of Vimovo tablets which remain RED-RED. Vimovo is comparatively priced to other NSAID/ gastro-protection combination products such as Arthrotec and Axorid. Ketoprofen/omeprazole (Axorid) tablets have already been designated RED-RED for similar reasons to Vimovo (also ketoprofen is no longer a preferred NSAID on grounds of higher GI risk). Prescribing of diclofenac and diclofenac containing products (such as Arthrotec) needs to be kept under regular review due to the higher thrombotic risk with diclofenac.

Further guidance

NSAID Choice

In terms of product selection, low dose ibuprofen (e.g. 1200mg per day) has the lowest gastro-intestinal (GI) risk of standard NSAIDs. Low dose ibuprofen and naproxen (1000mg per day) have a lower thrombotic risk than other NSAIDs and coxibs; epidemiological data does not suggest an increased risk of myocardial infarction (MI) with either agent. Prescribers should consider low dose ibuprofen first line whenever an NSAID is indicated. Naproxen represents a suitable second line alternative, although GI risk is higher.

Concurrent NSAID/PPI prescribing and PPI choice

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. An expensive

branded PPI such as esomeprazole (Nexium) is not appropriate for concurrent PPI therapy due to the excessive cost (see below).

Drug	Dose	Cost 28 days
Ibuprofen tablets	400mg to 800mg three times daily	£1.70 to £3.40
Naproxen tablets	500mg twice daily	£3.30
Naproxen tablets EC	500mg twice daily	£4.45
Omeprazole capsules	20mg daily	£1.36
Lansoprazole capsules	15 to 30mg daily	£1.02 to £1.56
Pantoprazole tablets	20mg daily	£1.18
Esomeprazole tablets(Nexium)	20mg daily	£18.50
Naproxen 500mg/esomeprazole 20mg tablets (Vimovo)	One tablet twice daily	£13.95
Diclofenac 50mg/ misoprostol 200mcg (Arthrotec 50) SR tablets	One tablet two to three times daily	£11.18 - £16.77
Diclofenac 75mg/ misoprostol 200mcg (Arthrotec 75) SR tablets	One tablet twice daily	£14.77
Ketoprofen 100mg/omeprazole 20mg (Axorid) tablets	One capsule twice daily	£12.88
Naproxen 500mg/misoprostol 200mcg tablets (Napratec)	One tablet of each drug taken twice daily	£23.76

NEW DRUG ASSESSMENT: *RISPERIDONE INJECTION (RISPERDAL CONSTA)*

Risperidone is a second-generation antipsychotic drug that was first formulated as the long acting intramuscular injection (Risperdal Consta) in 2003. Risperdal Consta is licensed for the maintenance treatment of schizophrenia in patients stabilised with oral antipsychotics. The original supporting evidence for Risperdal Consta came from two 12 week randomised controlled trials and one 12 month trial which demonstrated that the long acting IM injection was at least as effective as oral risperidone and more effective than placebo in controlling both positive and negative symptoms in schizophrenia. This resulted in Risperdal Consta becoming established as an option for the management of schizophrenia in those patients who were unable to comply with oral therapy. More recent studies have demonstrated that, following a switch to risperidone long acting injection, the number of patients requiring hospitalisation, the number of hospital admissions and the length of stay decreased regardless of previous antipsychotic treatment.

Risperdal Consta has a good safety and tolerability profile with a low propensity to cause physical health related adverse events. Fortnightly injection allows regular contact, engagement, assessment and monitoring of mental and physical health. Compared with a conventional depot, there is a reduction in extrapyramidal and other side effects. One study found that twenty one percent fewer patients used anti-Parkinsonian drugs with Risperdal Consta that with zuclopenthixol.

However, treatment costs are high in comparison to other alternatives:

Drug	Daily dose range	Cost per dose	Cost (£) pa
Risperdal Consta	**25mg every 2 weeks**	**£79.69**	**£2,071.94**
	37.5mg every 2 weeks	**£111.32**	**£2,894.32**
	50mg every 2 weeks	**£142.76**	**£3,711.76**
flupentixol	50 every 4 weeks	£1.53	£19.89
flupentixol	300mg every 2 weeks	£6.01	£156.26
fluphenazine deconate	12.5mg -100mg every 2 – 5 weeks	12.5mg £1.30 25mg £2.25 50mg £4.44 100mg £8.79	£33.80– £228.54

haloperidol deconate	50-300mg every 4 weeks	50mg £3.81 100mg £5.05	£49.56 -£197.03
zuclopenthixol	200mg every 1-4 weeks	£1.98	£ 25.74- £102.96
zuclopenthixol	500mg every 1-4 weeks	£3.64	£47.32 – £189.28
risperidone tablets	4-6mg daily Max dose 16mg		£14.01 - £25.84 £56.06

PACEF Recommendation:
Following a detailed review of the evidence, PACEF are convinced that risperidone long acting injection (Risperdal Consta) is appropriate for prescribing in primary care, subject to the development of shared care guidelines. The increased cost is offset by the reduction in hospital admissions and the length of stay. Designation: AMBER. The SCG is in development and will be made available to prescribers early in 2012 subject to PACEF approval. PACEF acknowledge that commissioning arrangements around depot antipsychotics vary between CCGs and that shared care may not be considered appropriate in all areas.

NICE TECHNOLOGY APPRAISAL 231: *AGOMELATINE FOR THE TREATMENT OF MAJOR DEPRESSIVE EPISODES* (TERMINATED APPRAISAL) (JULY 2011)

Agomelatine is a novel antidepressant agent that acts at both melatonergic and 5-HT_{2C} receptors; the mechanism by which this alleviates depression remains unclear at present. The product is licensed for the treatment of major depressive episodes in adults. PACEF have reviewed agomelatine for this indication on two occasions and have expressed concern over the quality of the trial data and the high cost of the product compared to other widely prescribed alternatives. NICE have recently appraised the product and have concluded that they cannot recommend agomelatine for use in the NHS for the treatment of major depressive episodes because no evidence submission was received from the manufacturer, Servier.

As part of the local response to this NICE TA, PACEF are required to consider the reasons behind the NICE decision. Servier did not make an evidence submission to NICE on the basis that NICE Clinical Guideline 90 *Depression in adults* (2009) recommends generic SSRIs first line followed by a different SSRI or a better tolerated newer generation agent second line. The manufacturer noted that the majority of clinical trial evidence for agomelatine was as a first line treatment and was not against the full range of comparators included in the scope. This precluded the manufacturer from developing an economic case.

Despite the comparatively high cost, the original PACEF review identified short-term, small-scale clinical trials against sertraline, fluoxetine and venlafaxine that showed at least comparable efficacy and possible benefits in terms of tolerability (see *PACE Bulletin*, Vol 3 No 11 (October 2009)). A subsequent PACEF review in October 2010, considered the side effect profile and the monitoring requirements (i.e. LFTs at initiation, 6 weeks, 12 weeks, 24 weeks and thereafter when indicated) (see *PACE Bulletin* Vol 4 No 20 (November 2010). From this, agomelatine emerged as having a neutral effect on body weight, heart rate and BP with no identified discontinuation symptoms on abrupt withdrawal.

PACEF Recommendation:
PACEF are mindful of the NICE recommendation, but have also considered the reasons behind the decision as part of local implementation. After careful

consideration of the two previous PACEF assessments of the product and the NICE TA, PACEF have decided to continue to support existing local arrangements where agomelatine is designated RED for this indication (i.e. it can be prescribed solely within LPFT for patients with major depressive disorder). Prescribers are reminded that agomelatine is not approved for use in primary care and should not be prescribed even in response to a request to continue secondary care initiated prescribing from a LPFT mental health specialist.

NICE TECHNOLOGY APPRAISAL 232: *RETIGABINE FOR THE ADJUNCTIVE TREATMENT OF PARTIAL ONSET SEIZURES IN EPILEPSY* (JULY 2011)

Key Recommendations

Retigabine is recommended as an option for the adjunctive treatment of partial onset seizures with or without secondary generalisation in adults aged 18 years and older with epilepsy, only when previous treatment with carbamazepine, clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, sodium valproate and topiramate has not provided an adequate response, or has not been tolerated.

PACEF Recommendation:
Retigabine tablets (Trobalt) are designated AMBER within licensed indications and restrictions as specified by NICE. No shared care guideline is required. ULHT have informed PACEF that the role of this product is likely to be extremely limited. AMBER status requires initiation only by or at the request of a specialist.

NICE TECHNOLOGY APPRAISAL 235: *MIFAMURTIDE FOR THE TREATMENT OF OSTEOSARCOMA (OCTOBER 2011)*

Key Recommendations

Mifamurtide in combination with postoperative multi-agent chemotherapy is recommended within its licensed indication as an option for the treatment of high-grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection in children, adolescents and young adults and when mifamurtide is made available at a reduced cost to the NHS under the patient access scheme.

PACEF Recommendation:
Mifamurtide (Mepact) intravenous infusion is licensed for high-grade, resectable, non-metastatic osteosarcoma after complete surgical resection in patients 2 to 30 years of age at initial diagnosis. It is used in combination with chemotherapy. It has been designated RED for this indication.

NEW TRIALS IN BRIEF

Tailored letters to patients can help to reduce benzodiazepine use

A systematic review and meta-analysis of three RCTs (615 patients; mean age > 60) in UK general practice found that a tailored letter can help long term benzodiazepine users to reduce or stop treatment at 6 months without adverse consequences. The 'number needed to post' for the tailored letter was about 12 (i.e. for every twelve letters sent one additional person stopped using benzodiazepines at 6 months).

PACEF Comment:
The use of benzodiazepine and related hypnotics in Lincolnshire general practice is higher than the national average. In Quarter 1 2010/11, the weighted volume of use of benzodiazepines and Z drugs in Lincolnshire was 2.153 Average Daily Quantities per STAR-PU compared to an England average of 1.682. NICE guidance on insomnia states that hypnotics should be used in the lowest dose possible for no more than 4 weeks with benzodiazepines, or 2 to 4 weeks with Z drugs. When a hypnotic is indicated, the drug of lowest acquisition cost should be used (i.e. zopiclone tablets). NICE guidance on generalised anxiety disorder recommends that benzodiazepines should only be used as a short-term measure during crises. This systematic review reminds us that long term use of hypnotics can be reduced in some patients by the simple act of issuing a tailored letter to the patient expressing concern about their long term use, their potential side effects and giving advice on how to gradually and safely reduce or stop them.

Reference:
Mugunthan K et al. Minimal interventions to decrease long-term use of benzodiazepines in primary care – a systematic review and meta-analysis. *Br J Gen Pract* 2011; DOI: 10.3399/bjgp11X593857.

Topical antibiotics for acute infective conjunctivitis: to treat or not to treat?

An individual patient data meta-analysis of three primary care based RCTs (n=622) found a small, statistically significant benefit of topical antibiotics in acute infective conjunctivitis, compared with control (80% of pts receiving antibiotics and 71% of controls were cured at day 7, NNT of 13). The subgroups that significantly benefited from antibiotics were those with a purulent discharge and those with a mild severity red eye. Most people recovered by day 7 regardless of whether an antibiotic was used, even when the cause was bacterial.

PACEF Comment:
Health Protection Agency advice recommends that acute infective conjunctivitis should only be treated if severe as most infections are viral or self-limiting. In line with this, prescribing rates of topical antibiotics have been falling, although availability of chloramphenicol eye drops OTC from pharmacies may be driving increasing use through another route. This meta-analysis confirms that most patients recover from acute infective conjunctivitis by day 7 regardless of whether they receive antibiotics or not. Patient subgroups identified as gaining a (limited) benefit from antibiotics were those with a purulent discharge and mild severity of red eye. This may be because viral and allergic conjunctivitis and episcleritis are more likely to be associated with a more severe red eye. Prescribers and community pharmacists can use this data to inform patient consultations and to provide reassurance about the self-limiting nature of this condition.

SHARED CARE GUIDELINE: *DRONEDARONE FOR THE TREATMENT OF NON-PERMANENT ATRIAL FIBRILLATION* (NOVEMBER 2011)

In response to the continuing emergence of safety concerns around the use of dronedarone, it has become necessary to revise local shared care arrangements. In consultation with ULH Cardiology a new edition of the SCG has been produced and is now available on the NHS Lincolnshire website. The full title of the revised SCG is:

- *Dronedarone for the treatment of patients with non-permanent atrial fibrillation after other anti-arrhythmic medicines have been considered* (November 2011).

Copies should be issued by the initiating cardiologists in conjunction with every request for a GP to participate in shared care with dronedarone. All patients currently prescribed dronedarone in county should be under shared care and specialist supervision. The full text SCG is available on the NHS Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF. Copies are also available on request from Cathy Johnson, the Interface Lead Pharmacist (cathy.johnson@lpct.nhs.uk).

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (OCTOBER/DECEMBER 2011)

CITALOPRAM AND ESCITALOPRAM ASSOCIATED WITH DOSE-DEPENDENT QT INTERVAL PROLONGATION

In *PACE Bulletin*, Vol 5 No 18 (December 2011), we published preliminary guidance on the role of citalopram in the wake of clinical evidence that revealed dose dependent QT interval prolongation extending down into the therapeutic dose range. In response to this evidence Lundbeck announced a series of changes to the Summary of Product Characteristics for Cipramil as follows:

- The recommended maximum dose in adults has been reduced from 60mg to 40mg daily. Similarly the recommended maximum dose in the elderly has dropped from 40mg to 20mg. In patients with reduced hepatic function the recommended maximum dose has been reduced from 30mg to 20mg.
- Contra-indications have been expanded to include known QT interval prolongation or congenital long QT syndrome. Co-administration with other drugs known to prolong the QT interval is also contra-indicated (see below).
- Caution is advised in patients at higher risk of developing Torsade de Pointes (TdP) (e.g. those with congestive heart failure, recent MI, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or medicines).

Following on from this, Lundbeck published a further set of SPC changes for escitalopram (Cipralex) published in a 'Dear Healthcare Professional' letter of December 5th 2011. This letter emphasised the association between escitalopram and dose-dependent QT interval prolongation and publicised the following SPC changes:

- In elderly patients (>65 years) the maximum dose of escitalopram is now reduced to 10mg daily.
- The maximum dose of escitalopram for adults less than 65 years remains 20mg daily.
- Contra-indications have been expanded to include known QT interval prolongation or congenital long QT syndrome. Co-administration with other drugs known to prolong the QT interval is also contra-indicated (see below).
- Caution is advised in patients at higher risk of developing TdP (e.g. those with uncompensated heart failure, recent MI, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or medicines).
- Patients should be advised to contact a healthcare professional immediately if they experience an abnormal heart rate or rhythm while taking escitalopram.

Other drugs known to prolong the QT interval include: Class IA and III antiarrhythmics (e.g. amiodarone, dronedarone, quinidine), antipsychotics (e.g. pimozide, haloperidol), tricyclic antidepressants, some antimicrobial agents (e.g. moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment, particularly halofantrine), some antihistamines (e.g. astemizole, mizolastine) and some antiretrovirals (e.g. ritonavir, saquinavir, lopinavir)

Most recently, the MHRA have issued their guidance on the use of citalopram and escitalopram in the December issue of *Drug Safety Update* (Vol 5 Issue 5). They emphasize that QT interval prolongation was already known to be an established risk with both of these medicines which are closely related chemically. Citalopram is a racemic mixture of both R and S citalopram; escitalopram is the S enantiomer of citalopram. They detail the SPC changes as stated above and give the following advice to healthcare professionals:

- Patients who currently take doses of citalopram or escitalopram higher than the new recommended daily maximum should have their treatment reviewed. Maximum daily doses are summarized below:

	Adults	Adults > 65 years	Adults with hepatic impairment
Citalopram	40mg*	20mg*	20mg*
Escitalopram	20mg	10mg*	10mg

* New (restricted) maximum daily dose.

- Citalopram and escitalopram should not be used in patients with congenital long QT syndrome or known pre-existing QT interval prolongation or in combination with other medicines known to prolong the QT interval (see above).
- The balance of benefits and risks of citalopram and escitalopram should be considered carefully, particularly at higher dosage, in patients with pre-existing risk factors for QT interval prolongation (e.g. those with uncompensated heart failure, recent MI, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or medicines).
- In patients with cardiac disease, an ECG review should be considered before treatment with citalopram or escitalopram.
- Electrolyte disturbances (e.g. hypokalaemia and hypomanesaemia) should be corrected before treatment with citalopram and escitalopram. Monitoring of serum magnesium is advised, particularly in elderly patients, who may be taking diuretics or PPIs.
- If cardiovascular symptoms, such as palpitations, vertigo, syncope or seizures develop during treatment, cardiac evaluation including an ECG should be undertaken to exclude a possible malignant cardiac arrhythmia.
- If QTc interval is >500 milliseconds, treatment should be withdrawn gradually. If QTc interval duration is between 480 milliseconds and 500 milliseconds, the balance of benefits and risks of continued treatment should be carefully considered, alongside options for dose reduction or gradual withdrawal.

PACEF Recommendations:

A local review of published case reports, clinical papers and Committee on Safety of Medicines (CSM) reports has revealed that QT interval prolongation and TdP have been seen with *all* SSRIs and could be a class effect. However, the small number of reports suggests that this problem rarely becomes symptomatic and then usually only in overdose. Tricyclic antidepressants are also known to exhibit this effect and are thought to be more commonly

associated with QT interval prolongation than SSRIs. As a result of this, citalopram continues to be designated GREEN and can continue to be prescribed subject to the constraints defined by the more restrictive SPC and MHRA guidance detailed above. PACEF has long harboured reservations about the use of escitalopram, predominantly on grounds of its high cost in comparison to generic citalopram. Existing advice from *PACE Bulletin* (Vol 4 No 5 (May 2010)) still stands. Escitalopram may be considered second line for people with severe depression who have shown an antidepressant response to other SSRIs, but have been unable to tolerate side-effects. Prescribers should ensure that escitalopram is not used first line or to treat people who have failed to respond to other SSRIs. Within this second line context, escitalopram (Cipralex) remains GREEN subject to the constraints defined by the more restrictive SPC and MHRA guidance detailed above. Where the required dose adjustments to citalopram or escitalopram result in reduced treatment effectiveness or relapse, consideration will need to be given to alternative therapies. Further guidance in relation to alternative therapies is in preparation in conjunction with Lincolnshire Partnership Foundation Trust.

References:
Lundbeck Ltd, *Association of Cipramil (citalopram hydrobromide) with dose-dependent QT interval prolongation* (24th October 2011)
Lundbeck Ltd, *Association of escitalopram (Cipralex) with dose-dependent QT interval prolongation* (5th December 2011)
MHRA, Citalopram and escitalopram: QT interval prolongation, *Drug Safety Update*, Vol 5 Issue 5 (December 2011)

BUCCAL MIDAZOLAM (BUCCOLAM) NEW AUTHORISED MEDICINE FOR PAEDIATRIC USE – CARE NEEDED WHEN TRANSFERRING FROM UNLICENSED FORMULATIONS

Buccal midazolam (Buccolam) is a new licensed treatment for prolonged acute convulsive seizures which is due to be launched in the UK within the next couple of months. It provides a potential alternative to rectal diazepam. Previously, buccal midazolam was only available in a range of unlicensed formulations, including Buccolam.

The MHRA advise that care should be taken when transferring patients to the new formulation. Several factors need to be considered when transferring patients to the licensed Buccolam preparation:

- Buccolam is half the strength of some of the alternative unlicensed preparations
- Buccolam contains the hydrochloride salt whereas some other products contain the maleate salt. The maleate salt may be better absorbed from the buccal cavity.
- Midazolam should be used with caution in patients with chronic respiratory insufficiency as it depresses respiratory function.
- Midazolam may accumulate in patients with chronic renal failure or impaired hepatic or cardiac function and should therefore be used with caution in these individuals.
- The most common adverse reactions in clinical trials were sedation, somnolence, depressed levels of consciousness, respiratory depression, nausea and vomiting.

PACEF Comment:
Buccal midazolam (Buccolam) will be evaluated by PACEF shortly after launch. Further guidance will be issued once this evaluation has been completed.

CALCIUM AND VITAMIN D: STUDIES OF CARDIOVASCULAR RISK

In *PACE Bulletin* Vol 4 No 18 (October 2010), we discussed a recent meta-analysis in the *British Medical Journal* that identified a 30% increase in the relative risk of myocardial infarction associated with calcium supplements compared with placebo in post menopausal women who used calcium supplements to prevent osteoporotic fracture. This MA also reported non-significant increases in the incidence of death and stroke. The same researchers have also recently published a re-analysis of data from a large RCT (the Women's Health Initiative study (WHI)) and a further MA of trials of calcium with or without vitamin D. Overall the re-analysis of the WHI trial did not provide conclusive evidence of clinically significant harm. **This re-analysis has been reviewed by the Committee on Human Medicines (CHM) who have advised that the data does not provide convincing evidence that calcium plus vitamin D supplements are associated with an increased risk of cardiovascular events.**

In response to this the MHRA have issued the following advice to healthcare professionals:

- Prescribers should consider the potential risks of using calcium and vitamin D for the prevention of osteoporotic fractures on an individual basis in line with NICE guidance. Prescribing of these supplements should be offered to all post menopausal women receiving osteoporosis treatment unless the clinician is confident that the patient has an adequate calcium intake and is vitamin D replete.
- The National Osteoporosis Society advises that increasing dietary intake in those with low intakes of calcium and vitamin D is considered preferable to supplements. They also advise that supplementation may be warranted, but needs to be done with consideration based on dietary intake.

PACEF Recommendations

(1) There is no convincing evidence that calcium and vitamin D supplements are associated with an increased risk of CV events and existing PACEF advice on calcium and vitamin D supplementation still stands (see below).
(2) Calcium supplementation (without vitamin D) is known to have only modest effects on bone density and, given that this data suggests evidence of harm, calcium supplementation alone should not be used in the management of osteoporosis.
(3) People using calcium supplements (without vitamin D) to improve bone health should be advised to use dietary change to ensure an adequate intake of calcium or consider the use of supplements containing both calcium and vitamin D.

PACEF Advice on Calcium and Vitamin D Supplementation

(1) There is strong evidence to suggest that elderly people living in institutionalised care are likely to benefit from calcium and vitamin D supplementation. The best evidence is around daily doses of 1200mg of calcium and 800i.u. of vitamin D. Evidence suggests that this can significantly reduce the risk of hip fracture, non-vertebral fracture and falls. It is strongly recommended that all ambulatory patients over the age of 65 currently resident in sheltered accommodation or care homes should be prescribed calcium and vitamin D. Prescribers are encouraged to review all patients in care homes and sheltered accommodation to ensure that calcium and vitamin D supplementation is

prescribed for the ambulatory over 65s unless there are compelling reasons not to do so.
(2) Calcium and vitamin D should be prescribed for people on or commencing systemic corticosteroid therapy at any dose for 3 months or longer.
(3) All women on treatment for the primary or secondary prevention of osteoporotic fragility fractures should be prescribed calcium and vitamin D unless dietary intake is considered to be adequate.
(4) Only calcium and vitamin D formulations containing an evidence based dose of each component should be prescribed (i.e. at least 1000mg of calcium and 800i.u. of vitamin D daily). First line preferred products are Accrete D3 tablets, Adcal-D3 Chewable tablets, Adcal D3 caplets, Calceos Chewable tablets and Natecal D3 Chewable tablets (see cost comparison below).

Product	Dose	Price (28 days)	Flavour
Accrete D3 tablets (calcium 600mg/vit D 400i.u.)	**1 tablet twice daily**	**£3.36**	
Adcal –D3 Chewable tablets (calcium 600mg/ vit D 400i.u.)	**1 tablet twice daily**	**£3.65**	**Lemon or Fruit**
Adcal D3 caplets (calcium 300mg/vit D 200i.u.)	**2 tablets twice daily**	**£3.65**	
Adcal-D3 Dissolve Effervescent tablets (calcium 600mg/vit D 400i.u.)	1 tablet twice daily	£4.99	Lemon
Cacit D3 Effervescent granules (calcium 500mg/ vit D 440i.u.)	2 sachets daily	£7.58	Lemon
Calceos Chewable tabs (Calcium 500mg/ vit D 400i.u.)	**1 tablet twice daily**	**£3.38**	**Lemon**
Calcichew D3 Forte Chewable tablets (calcium 500mg, Vit D 400i.u.)	1 tablet twice daily	£3.96	Lemon
Calcichew D3 500mg/400iu caplets (calcium 500mg, Vit D 400i.u.)	1 tablet twice daily	£4.16	
Calfovit D3 Sachets (calcium 1200mg/Vit D3 800i.u.)	1 sachet daily	£4.04	Lemon
Natecal D3 chewable tablets (calcium 600mg/vit D 400i.u.)	**1 tablet twice daily**	**£3.39**	**Aniseed/peppermint**
Sandocal + D 600 effervescent tablets (calcium 600mg/vit D 400iu)	1 tablet twice daily	£4.90	Orange
Sandocal + D 1200 effervescent tablets (calcium 1200mg/vit D 800iu)	1 tablet daily	£4.04	Orange

Prices are compiled from *MIMS*, December 2011. Appropriate first line options are highlighted in bold.

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Stephen Gibson
Head of Prescribing and Medicines Management
NHS Lincolnshire

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