NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

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What's new this month?

- **Emerging evidence suggests a link between the use of pioglitazone and bladder cancer. Current advice from the American Food and Drugs Administration and the European Medicines Agency is reviewed and advice given (see page 2).**
- **The new orodispersible formulation of vardenafil (Levitra) for erectile dysfunction has not been approved for prescribing. Designation: RED-RED (see page 4).**
- **A new aminoglycoside antibiotic eye drop containing tobramycin (Tobravisc) has not been approved for prescribing. Designation: RED-RED (see page 4).**
- **A new topical retinoid/benzoyl peroxide gel formulation (Epiduo) has been approved for use (see page 6).**
- **NICE gave reviewed a range of treatments for intermittent claudication in peripheral arterial disease and have endorsed only naftidrofuryl oxalate for use within the NHS. Cilostazol, pentoxifylline and inositol nicotinate are no longer recommended for this indication (see page 7).**
- **A shared care guideline for the use of dronedarone in non-permanent AF.**

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

SUMMARY OF PACEF DECISIONS: JUNE 2011 UPDATE

Drug	Indication(s)	Traffic Light Status
Adapalene and benzoyl peroxide gel 0.1%/2.5% (Epiduo)	Treatment of acne vulgaris with comedones, papules and pustules	GREEN
Cilostazol tablets 50mg and 100mg	Improvement of maximal and pain	RED-RED

(Pletal)	free walking distances in patients with intermittent claudication who do not have rest pain or evidence of peripheral tissue necrosis	
Inositol nicotinate 500mg and 750mg tablets (Hexopal/Hexopal Forte)	Intermittent claudication	RED-RED
Naftidrofuryl 100mg capsules (generic/ Praxilene)	Peripheral vascular disorders	GREEN Generic prescribing preferred
Pentoxifylline tablets modified release 400mg (generic/Trental)	Peripheral vascular disorders	RED-RED
Sildenafil film coated tablets (Viagra) 25mg, 50mg and 100mg	Treatment of erectile dysfunction	GREEN Subject to restriction under *Drug Tariff* Part XVIIIB
Tadalafil film coated tablets (Cialis) 2.5mg, 5mg, 10mg, 20mg	Treatment of erectile dysfunction	GREEN Subject to restriction under *Drug Tariff* Part XVIIIB
Tobramycin 3mg/ml eye drops (Tobravisc)	Superficial bacterial eye infections	RED-RED
Vardenafil film coated tablets (Levitra) 5mg, 10mg and 20mg	Treatment of erectile dysfunction	GREEN Subject to restriction under *Drug Tariff* Part XVIIIB
Vardenafil orodispersible tablets (Levitra) 10mg	Treatment of erectile dysfunction	RED-RED

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care.**

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.**

PIOGLITAZONE AND BLADDER CANCER

- The American Food and Drug Administration (FDA) have reviewed the safety of pioglitazone (Actos) citing concerns over a possible link to bladder cancer.
- The FDA review is based on an ongoing 10-year observational cohort study as well as a nested, case-control study of the long-term risk of bladder cancer in 193,000 patients with diabetes in the Kaiser Permanente Northern California health plan. A preliminary analysis of this data showed an increasing risk of bladder cancer with pioglitazone which reached statistical significance after 24 months.
- A new analysis using the FDA adverse event reporting system showed similar trends.
- Their conclusion is that there is no overall increased risk of bladder cancer with pioglitazone, but there is an increased risk in patients with the longest exposure and the highest cumulative dose.
- On the 15th of June 2011 the FDA published their findings stating that the use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer. They have asked for this risk to be detailed in the 'Warnings and Precautions' section of the product's label. They have also warned patients about the increased risk and the need to avoid pioglitazone if

receiving treatment for bladder cancer. Increased vigilance for the symptoms of bladder cancer during pioglitazone therapy is also advocated.

- The French drug regulatory authority (AFSSAPS) suspended the marketing authorisation of pioglitazone in France on June 9th 2011. This was in response to the findings of a recent epidemiological study conducted in France that suggested an increased risk of bladder cancer. In response to this, the German regulatory authority recommended that no new patients should be started on pioglitazone therapy.
- The European Medicines Agency announced a review of pioglitazone safety in March 2011 and published guidance on the 21st of July. They continue to support the use of pioglitazone as a treatment option in patients with type 2 diabetes mellitus but acknowledge a small increased risk of bladder cancer with this drug. Prescribers are advised not to use pioglitazone containing medicines in patients with current or a history of bladder cancer or in patients with uninvestigated macroscopic haematuria. Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment. In particular the increasing risk with age should be considered both before initiation and as part of regular review. Prescribers should review the treatment of patients on pioglitazone after 3 to 6 months (and regularly thereafter) to ensure that only those deriving sufficient benefit should continue to take it.
- The EMA acknowledge the FDA position that the risk of bladder cancer in diabetic patients treated with pioglitazone is greatest in those treated for the longest duration and with the highest cumulative doses. However, they state that a possible risk after short-term treatment cannot be excluded.

PACEF Comment:

The EMA continue to support the use of pioglitazone as an option for the treatment of type 2 diabetes, but acknowledge the growing evidence for an increased risk of bladder cancer with this drug, particularly linked to long-term use. Prescribers should ensure that pioglitazone is not used in patients with active bladder cancer or in those with a prior history of bladder cancer. They should also review the risks and benefits in patients at increased risk of bladder cancer (e.g. the elderly as the risk of bladder cancer increases with age, current or past history of smoking, first degree relative with bladder cancer, occupational exposure to some occupational or chemotherapy agents such as cyclophosphamide; or previous radiation therapy to the pelvic region). At their next review, patient's should be made aware of the risk and encouraged to remain vigilant for key symptoms such as blood or red colour in the urine, urgent need to urinate, pain while urinating or pain in the lower back or lower abdomen. Prescribers should review the treatment of patients on pioglitazone after 3 to 6 months (and regularly thereafter) to ensure that only those deriving sufficient benefit should continue to take it. Patients who are already receiving pioglitazone should be reviewed both for risk factors associated with bladder cancer and also to assess that they are continuing to receive benefits from treatment. The NICE Clinical Guideline for the management of type 2 diabetes (CG87 May 2009) states that thiazolidinedione therapy should only continue if the person has had a beneficial metabolic response (i.e. a reduction of at least 0.5 percentage points in HbA_{1C} in six months). Any further advice from the MHRA will be reviewed in a future issue of the *Bulletin*.

NEW FORMULATION ASSESSMENT: *VARDENAFIL ORODISPERSIBLE TABLETS (LEVITRA)*

Vardenafil orodispersible 10mg tablets (Levitra) present the first orodispersible treatment for erectile dysfunction (ED). Vardenafil belongs to a class of drugs known as the phosphodiesterase (PDE5) inhibitors; other examples include sildenafil (Viagra) and tadalafil (Cialis). All three of the PDE5 inhibitors are designated GREEN on the Lincolnshire Traffic Light List and are approved for prescribing in primary care for those patients eligible for NHS funded ED treatment (see below). Of the three, tadalafil and sildenafil are the most widely prescribed in Lincolnshire; vardenafil use remains relatively low.

PACEF found no evidence to demonstrate that orodispersible vardenafil offers any advantage over the traditional film coated tablet formulation. No comparative head-to-head studies have been carried out between the standard film-coated tablets and the orodispersible formulation. Pharmacokinetic data reveals that orodispersible vardenafil has improved bioavailability over the film-coated tablet formulation, but this difference has not been found to be clinically significant.

A cost comparison of the different PDE5 inhibitors reveals that vardenafil orodispersible 10mg tablets are more expensive than the standard film-coated formulation:

Drug	Dose	Cost (£)
Vardenafil orodispersible tablets (Levitra)	**10mg**	**£17.88 (4 tabs)**
Vardenafil film coated tablets (Levitra)	10mg	£14.08 (4 tabs) £28.16 (8 tabs)
	5mg	£7.56 (4 tabs) £15.12 (8 tabs)
	20mg	£23.48 (4 tabs) £46.96 (8 tabs)
Sildenafil film coated tablets (Viagra)	25mg	£16.59 (4 tabs) £33.19 (8 tabs)
	50mg	£21.27 (4 tabs) £42.54 (8 tabs)
	100mg	£23.50 (4 tabs) £46.99 (8tabs)
Tadalafil film coated tablets (Cialis)	2.5mg (daily)	£54.99 (28 tabs)
	5mg (daily)	£54.99 (28 tabs)
	10mg	£26.99 (4tabs)
	20mg	£26.99 (4 tabs) £53.98 (8 tabs)

PACEF Recommendations:

The vardenafil orodispersible 10mg tablet (Levitra) is significantly more expensive than the standard film coated formulation and offers no clear additional benefit. As a result of this, the product is designated RED-RED. The PDE5 inhibitors (sildenafil, tadalafil and vardenafil) should only be prescribed on the NHS to treat ED in men who: (1) have diabetes, multiple sclerosis, Parkinson's disease, poliomyelitis, prostate cancer, severe pelvic injury, single gene neurological disease, spina bifida or spinal cord surgery; (2) are receiving dialysis for renal failure; (3) have had radical pelvic surgery, prostatectomy (including transurethral resection of the prostate) or kidney transplant; (4) are suffering severe distress as a result of impotence (prescribed in specialist centres only). Prescriptions should be marked 'SLS'; one treatment a week is

considered appropriate for most patients, although a GP may prescribe more at his/her discretion. Practices should review the appropriateness of prescribing of treatments for ED to ensure that all prescribing falls within the *Drug Tariff* approved indications for NHS treatment. Any patient currently receiving treatment for erectile dysfunction on the NHS that is not within *Tariff* criteria should be contacted and informed that their NHS prescription cannot be continued. Patients may seek referral to a specialist centre for ED related to severe distress, although this should not result in referral back to the GP to prescribe. Alternatively, private prescribing is appropriate for non-NHS approved indications. At present, sildenafil and vardenafil (film coated tablet *not* orodispersible) present the lowest cost first line preferred options; sildenafil is likely to assume preferred first line status following patent expiry (expected in 2013).

RAPID DRUG ASSESSMENT: *TOBRAMYCIN 3MG/ML EYE DROPS (TOBRAVISC)*

Tobramycin 3mg/ml eye drops (Tobravisc) present a new aminoglycoside antibacterial eye preparation licensed for the topical treatment of superficial bacterial infections of the eye (e.g. conjunctivitis caused by tobramycin susceptible bacteria). For most people, use of a topical antibiotic will make little difference to recovery, although an antibacterial eye preparation is indicated if infective conjunctivitis is severe. Standard local and national guidance (from the Health Protection Agency and the *BNF*) recommends chloramphenicol eye drops (and eye ointment) as the preferred first line treatment; fusidic acid 1% gel is recommended as a second line alternative. Aminoglycoside eye drop preparations present a possible third line option with local microbiologists preferring gentamicin eye drops where a topical aminoglycoside is indicated. A cost comparison between tobramycin 3mg/ml eye drops and alternative aminoglycoside eye preparations appears below:

Drug	Daily dose range	Cost (£) per bottle
Tobramycin 3mg/ml eye drops (Tobravisc)	1 drop twice daily for 6-8 days. For severe infection use 1 drop four times daily on day 1.	£4.74 (5ml)
Gentamicin 0.3% eye drops (Genticin)	1-2 drops up to 6 times daily. For severe infection initially 1-2 drops every 15-20 minutes reducing frequency once infection is controlled.	£2.13 (10ml)
Neomycin 0.5% eye drops (3,500 units/ml)	Frequency dependent on severity of infection	£3.11 (10ml)*
Neomycin 0.5% eye ointment (3500 units/ml)	Frequency dependent on severity of infection	£2.44 (3g)*
Neosporin eye drops (neomycin+ polymyxin + gramicidin)	1-2 drops two to four times daily or more frequently if required.	£4.86 (5ml)

* Unlicensed special: price will vary depending on supplier.

From this, tobramycin eye drops emerge as significantly more expensive that gentamicin.

PACEF Recommendation:
Due to the increasing prevalence of bacterial resistance to antibiotics, microbiologists are advising clinicians to adhere to recommendations made by the HPA when treating bacterial conjunctivitis. Within this context, aminoglycoside eye formulations are designated as a possible third line option with gentamicin eye drops identified as the preferred preparation. Tobramycin eye drops offer no advantage over gentamicin eye drops and are over twice the price. As a result of this, tobramycin 3mg/ml eye drops (Tobravisc) are designated RED-RED.

RAPID DRUG ASSESSMENT: *ADAPALENE AND BENZOYL PEROXIDE GEL 0.1%/2.5% (EPIDUO)*

Adapalene and benzoyl peroxide gel 0.1%/2.5% (Epiduo) is a topical retinoid/keratolytic combination product licensed for the treatment of acne vulgaris when comedones, papules and pustules are present. Two randomised controlled trials involving a total of 2385 patients have shown that Epiduo provides a greater net benefit in patients with all grades of acne than either single component benzoyl peroxide (BPO) or adapalene therapy. There are no comparative studies between Epiduo and combination adapalene/BPO therapy (prescribed as separate components) or between Epiduo and any other topical retinoid or topical antibiotic formulation.

Standard treatment approaches advocate topical retinoid and benzoyl peroxide (BPO) combination therapy in moderate acne as an alternative to topical or oral antibiotic therapy. A recent review in the *Drug and Therapeutics Bulletin* has highlighted concerns over the increasing incidence of resistance to topical and oral antibiotics and the necessity to limit their use in acne (DTB, Vol 48. No 12 (December 2010)).

A cost comparison reveals that Epiduo is more expensive than its individual components prescribed separately, but comparably priced to topical antibiotic products such as Zineryt alcoholic solution and Duac gel:

Drug	**Daily dose range**	**Cost (£)**
Epiduo gel	Once daily	£17.91 (45g)
Topical retinoids		
Adapalene (Differin) Aqueous gel or cream formulations	Once daily	£11.40 (45g)
Isotretinoin (Isotrex)	Once or twice daily	£5.95 (30g)
Tretinoin (Retin A) 0.01% & 0.025%	Once or twice daily	£5.28 (60g)
Keratolytics		
Benzoyl peroxide 5% aqu gel (Acncide)	Once or twice daily	£5.44 (30g) £10.88 (60g)
Benzoyl peroxide 5% alc gel (Panoxyl)	Once daily	£1.89 (40g)
Benzoyl peroxide 10% alc gel (Panoxyl)	Once daily	£1.99 (40g)
Benzoyl peroxide 2.5% aqu gel (Panoxyl Aquagel)	Once daily	£1.76 (40g)
Benzoyl peroxide 5% aqu gel (Panoxyl Aquagel)	Once daily	£1.92 (40g)
Benzoyl peroxide 10% aqu gel (Panoxyl Aquagel)	Once daily	£2.13 (40g)
Benzoyl peroxide 5%	Once daily	£1.89 (40g)

cream		
Salicylic acid 2%(Acnisal)	Two to three times daily use as soap	£3.39 (177ml)
Topical antibiotic products		
Zineryt alcoholic solution(erythromycin + zinc)	Apply twice daily	£7.71 (30ml) £16.68 (90ml)
Duac gel (clindamycin & benzoyl peroxide)	Apply once daily	£9.95 (25g) £19.90 (50g)

PACEF Recommendation:

PACEF were concerned about the lack of comparative data between Epiduo and alternative therapies such as other topical retinoids, topical antibiotics and adapalene /BPO prescribed as separate components. The identified advantages of the product were a once daily treatment schedule and a possible synergistic effect from combination rather than single component therapy. Local dermatologists consider concordance with acne therapy to be a problem, particularly in younger patients; once daily combination therapy could help to improve this through simplification and through reduction in the number of prescription charges. In addition, alternative topical antibiotic preparations are comparably priced and associated with mounting concerns over increasing antibiotic resistance. In view of these factors and despite some reservations over the incomplete evidence base, PACEF designated adapalene and benzoyl peroxide gel 0.1%/2.5% (Epiduo) as GREEN.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 223: *CILOSTAZOL, NAFTIDROFURYL OXALATE, PENTOXIFYLLINE AND INOSITOL NICOTINATE FOR THE TREATMENT OF INTERMITTENT CLAUDICATION IN PEOPLE WITH PERIPHERAL ARTERIAL DISEASE* (MAY 2011)

Key Recommendations

- Naftidrofuryl oxalate is recommended as an option for the treatment of intermittent claudication in people with peripheral arterial disease for whom vasodilator therapy is considered appropriate after taking into account other treatment options. Treatment with naftidrofuryl oxalate should be started with the least costly licensed preparation.
- Cilostazol, pentoxifylline and inositol nicotinate are not recommended for the treatment of intermittent claudication in people with peripheral arterial disease.
- People currently receiving cilostazol, pentoxifylline and inositol nicotinate should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

A cost comparison reveals that generic naftidrofuryl oxalate is the least costly licensed naftidrofuryl preparation:

	Dose	**Cost/28 days**
Naftidrofuryl oxalate capsules 100mg (generic)	100mg to 200mg three times daily	£4.68 to £9.36
Naftidrofuryl oxalate capsules 100mg (Praxilene)	100mg to 200mg three times daily	£8.10 to £16.20
Cilostazol tablets 100mg (Pletal)	100mg twice daily	£35.31

Inositol nicotinate 750mg tablets (Hexopal Forte)	1.5g twice daily	£51.03
Pentoxifylline tablets 400mg (Trental)	400mg two to three times daily	£12.24 to £18.37

Prescribing data for January to March 2011 reveals that we currently spend £15,000 per quarter on these drugs in Lincolnshire (£60,000pa). Of this, naftidrofuryl constitutes 59% of the volume, but only 24% of the cost:

	Items	**Actual Cost**
Naftidrofuryl oxalate	663	£3,646
Cilostazol	134	£4,075
Inositol nicotinate	131	£4,503
Pentoxifylline	194	£2,767
Total	1,122	£14,991

PACEF Recommendation:
Naftidrofuryl oxalate is designated GREEN for the treatment of peripheral vascular disease (PVD). All prescribing of naftidrofuryl should be generic. Cilostazol is designated RED-RED for the treatment of intermittent claudication in peripheral arterial disease. Pentoxifylline and inositol nicotinate are designated RED-RED for PVD. No new patients should be initiated on cilostazol (Pletal), pentoxifylline (Trental) or inositol nicotinate (Hexopal/Hexopal Forte), although existing patients can continue until considered appropriate to stop.

NEWS IN BRIEF

NEW GUIDELINE ON ATOPIC ECZEMA

The Scottish Intercollegiate Guidelines Network (SIGN) have issued a new guideline on atopic eczema. Key points are as follows:

- Patients should have ongoing treatment with emollients (at least 2-4 times daily, even when eczema is under control), including during concurrent treatment with topical corticosteroids.
- Patients should be advised to apply topical corticosteroids once daily. For those with moderate to severe disease with frequent relapses, twice weekly topical corticosteroid maintenance therapy should be considered.
- Topical tacrolimus should only be considered in those aged 2 years or more, for the short term intermittent treatment of moderate to severe atopic eczema that has not been controlled by topical corticosteroids; or where there is a serious risk of important adverse effects from further topical corticosteroid use (particularly skin atrophy).
- Oral antibiotics are not recommended in the routine treatment of patients with non-infected atopic eczema.
- Patients should be referred to a dermatologist where there is uncertainty concerning the diagnosis; poor control of the condition or failure to respond to appropriate topical treatments; psychological upset or sleep problems; or recurrent secondary infection.

References:
DTB Select, 5 (June 2011)
SIGN, 2011, *Management of atopic eczema in primary care – a national clinical guideline* (available online at www.sign.ac.uk)

ARE ALL BETA BLOCKERS THE SAME IN HEART FAILURE?

A large observational cohort study has found differences in mortality rates between various beta blockers (BBs) used for heart failure (HF) suggesting that there may not be a class effect. This Canadian study looked at a cohort of 26,787 patients who had been admitted to hospital with a primary diagnosis of heart failure between 1998 and 2008 and had a BB prescription dispensed within 90 days of discharge. The commonly prescribed BBs were: metoprolol (54%), bisoprolol (24%), atenolol (10%), carvedilol (8%), and acebutolol (4%). The results suggest better survival with low lipid solubility BBs (acebutolol and atenolol) whereas RCTs and meta-analyses have demonstrated better outcomes with bisoprolol and carvedilol.

PACEF Comment:
NICE guidance for heart failure recommends BBs licensed for HF (i.e. bisoprolol, carvedilol and nebivolol). The *DTB* conclude that for patients with stable HF on a BB unlicensed for this condition, there is no urgent need to switch therapy.

Reference:
DTB Select, 5 (June 2011)

UPDATED MENINGOCOCCAL GUIDANCE

Ciprofloxacin is now recommended by the Health Protection Agency (HPA) as first line chemoprophylaxis for meningococcal disease in all age groups and in pregnancy. Rifampicin, the previous first line drug for meningococcal chemoprophylaxis remains an option. Ciprofloxacin is preferred because it is given as a single dose, does not interact with oral contraceptives and is more readily available from community pharmacies.

The HPA also recommend that children and young people with suspected bacterial meningitis who do not have a non-blanching rash should be transferred to secondary care without giving antibacterials, although these drugs should be given if urgent transfer to hospital is not possible.

For suspected meningococcal disease (meningitis with non-blanching rash or meningococcal septicaemia), the guidance advises that IM or IV benzylpenicillin should be given at the earliest opportunity, but should not delay transfer to hospital.

Reference:
HPA, Meningococcus and Haemophilus Forum 2011, *Guidance for public health management of meningococcal disease in the UK* (available online at www.hpa.org.uk)

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE (*JUNE 2011)

Bisphosphonates: atypical femoral fractures.

In 2008 a Europe wide review of bisphosphonates and atypical stress fractures concluded that alendronate use was associated with an increased risk of atypical stress fractures of the proximal femoral shaft and a warning to this effect was added to the alendronate product information. This data did not support or refute a class effect but the regulatory authorities decided to keep the issue under close review. A further Europe wide review has now been completed which included data from

published studies and pre-clinical studies, clinical trials and case reports provided by the license holders. The key findings were:

- Atypical femoral fractures have been reported rarely with bisphosphonate therapy, mainly in patients receiving long term treatment. This is now considered to be a class effect.
- Fractures can occur after minimal or no trauma. These can be slow to heal and patients will often present with groin or thigh pain associated with radiological features of a stress fracture before presenting with a completed femoral fracture.
- The absolute number of atypical fractures is far lower than the number of osteoporotic fractures prevented.

The MHRA have issued the following advice to healthcare professionals:

- Atypical femoral fractures are often bi-lateral therefore the contralateral femur should be examined in bisphosphonate treated patients who sustain a femoral fracture.
- Discontinuation of bisphosphonate therapy in patients with a suspected femoral fracture should be considered while their clinical condition is evaluated and should be based on an assessment of the benefits and risks of treatment for that individual.
- During bisphosphonate treatment patients should be encouraged to report any thigh, hip or groin pain. Any patient who presents with such symptoms should be evaluated for an incomplete femur fracture.
- The optimum duration of bisphosphonate treatment for osteoporosis has not been fully established. **The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks particularly after 5 years or more of use.**

Yasmin: risk of venous thromboembolism higher than levonorgestrel-containing pills.

Increased risk of venous thromboembolism (VTE) is associated with the use of combined oral contraceptives (COC). The incidence with desogestrel and gestodene containing pills has been studied extensively. Overall, women using pills containing desogestrel (Gedarel, Mercilon, Marvelon) or gestodene (Femodette, Millinette, Sunya, Femodene, Katya, Triadene) have a slightly higher risk of developing VTE than those who use levonorgestrel containing pills (Levest, Microgynon, Ovranette, Rigevidon, Logynon, TriRegol). The excess risk of VTE is highest during the first year a woman starts or switches their COC.

Yasmin contains a relatively new progestogen: drospirenone (first licensed in 2000). There have been reports of increasing VTE risk since then. The MHRA issued safety advice in April 2010 when studies suggested that the risk of VTE was estimated to be lower than that associated with desogestrel and gestodene containing COCs and higher than that attributed to the levonorgestrel containing pills. The MHRA advice at the time was brought to the attention of all prescribers in *PACE Bulletin* Volume 4 Number 7 (May 2010). A recent unpublished re-analysis of the data from one of the original studies comparing the VTE risk associated with various COC pills has strengthened these findings. The available evidence now clearly shows that the risk of VTE for drospirenone-containing COCs is higher than that for levonorgestrel-containing COCs and may be similar to that of the third generation COCs that contain

desogestrel or gestodene. Product information for Yasmin has been updated to reflect this evidence and to warn of the risk of VTE.

The MHRA have issued the following advice to healthcare professionals, outlining the risk of VTE's associated with COCs and advising:

- Levonorgestrel-containing pills have the lowest thrombotic risk and are the safest pill for women wanting to start or switch contraception. Prescribers should be aware of the updated information when discussing the most suitable type of contraceptive.
- Estimates are not precise, but for women who do not use contraceptive pills there is about 1 case of VTE per 10,000 each year. By comparison, in pregnancy you would expect 6 cases of VTE per 10,000 pregnancies per year. In healthy women taking Yasmin, you would expect 3/4 cases per 10,000 women per year. This is an increase from between 2/4 cases per 10,000 women as estimated from previous studies.
- Any prescribing decision should take into account each woman's personal risk factors and any contraindications including her experience with other contraceptive formulations.
- All COCs, including Yasmin should be prescribed with caution to obese women (BMI>30) or those with a higher baseline risk of VTE.

PACEF Comment:
Previous concerns on the increased risk of VTE's associated with Yasmin have been highlighted in the May 2010 edition of the *PACE Bulletin*. This largely concurs with previous risk assessment where Yasmin was perceived to carry a slightly lower risk of VTE compared with desogestrel and gestodene containing products but a higher risk of developing VTE compared to levonorgestrel containing products.

SHARED CARE GUIDELINES

PACEF have updated two existing shared care guidelines:

Unlicensed use of azathioprine for the treatment of Inflammatory Bowel Disease
Unlicensed use of mercaptopurine for the treatment of Inflammatory Bowel Disease
Dronedarone for the treatment of patients with non-permanent atrial fibrillation

Copies are available through the NHS Lincolnshire website (www.lincolnshire.nhs.uk) or from Cathy Johnson, Interface Lead Pharmacist on cathy.johnson@lpct.nhs.uk

EUROPEAN MEDICINES AGENCY SAFETY REVIEW OF DRONEDARONE (MULTAQ)

The EMA Committee for Medicinal Products for Human Use (CHMP) is reviewing the cardiovascular safety of dronedarone in response to data from the PALLAS study. This study was designed to investigate the role of dronedarone in patients with permanent AF and cardiovascular risk factors. Preliminary data showed an increased risk of CV side effects in the dronedarone arm such as CV death, stroke, and CV hospitalisation; in response to this the study was stopped. The EMA benefit-risk review of dronedarone is ongoing, but in the meantime prescribers are advised to monitor patients regularly to ensure that they do not progress from non-permanent

AF (the licensed indication) to permanent AF (a potential risk area emerging from PALLAS).

PACEF Recommendation:
Existing shared care guidelines for dronedarone in the treatment of patients with non-permanent AF remain in use subject to the ongoing EMA safety review. It is emphasized that the concerns raised by PALLAS are around patients with *permanent* AF which is not currently a licensed indication for dronedarone (Multaq). Within the context of licensed indications (i.e. non-permanent AF), dronedarone (Multaq) remains AMBER and subject to a shared care guideline. Dronedarone is licensed in clinically stable patients with previous or current non-permanent AF, to prevent recurrence or lower ventricular rate.
The Medicines And Healthcare products Regulatory Agency (MHRA) have already warned of the risk of cardiac failure and hepatotoxicity associated with dronedarone which was highlighted to all prescribers in the March 2011 edition of the *PACE Bulletin* (Vol 5, No 5). Patients should be advised to remain vigilant for the symptoms of heart failure (HF) or worsening of existing symptoms (e.g. weight gain, dependent oedema, increased dyspnoea). If HF develops or worsens, consider suspending or discontinuing dronedarone. Patients should also be advised to remain vigilant for the symptoms of liver injury (e.g. abdominal pain or discomfort, loss of appetite, nausea, vomiting, yellowing of the skin or whites of the eye, darkening of the urine, itching or fatigue). All prescribers should be reminded that patients currently receiving dronedarone should have liver function tests preformed before treatment, on a monthly basis for 6 months, at months 9 and 12 and periodically thereafter. This and other monitoring requirements are detailed in the Lincolnshire shared care guideline.

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