NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 3; Number 7 **June 2009**

What's new this month:

- **NHS Evidence has launched (see page 4).**
- **Fluticasone furoate nasal spray (Avamys) has not been approved for use (see page 4).**
- **NuvaRing has been approved for restricted use within Sexual Health Services (see page 5).**
- **Grazax has been reviewed again and the classification remains unchanged: RED-RED (see page 7).**
- **NICE have approved the use of rivaroxaban (Xarelto) for the prevention of venous thromboembolism after total hip or total knee replacement in adults (see page 10).**
- **NICE have issued clinical guidelines on the diagnosis and treatment of breast cancer (see pages 11 to 15)**
- **A shared care guideline on the use of anticholinesterase inhibitors in the treatment of moderately severe Alzheimer's disease has been agreed (see page 16).**

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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. Steps will be taken to ensure the widest possible distribution across NHS Lincolnshire and within United Lincolnshire Hospitals Trust (ULHT) and Lincolnshire Partnership Foundation Trust (LPFT). Both paper and electronic copies will be circulated initially with a view to evolving into complete electronic distribution as soon as we are confident that all key stakeholders can access E-mail. There are also plans to make all bulletins, guidelines, formularies, new product assessments, new trial assessments, care pathways and other PACEF publications available through the NHS Lincolnshire website.

SUMMARY OF PACEF DECISIONS: MAY 2009 UPDATE

Drug	Indication(s)	Traffic Light Status
Aliskiren (Rasilez) tablets	Licensed for the treatment of essential hypertension; used either as monotherapy or in combination with other antihypertensive agents.	AMBER Specialist initiation only; no formal shared care guideline is required at this stage.
Anastrozole (Arimidex) tablets	Licensed for: Adjuvant treatment of oestrogen receptor positive early invasive breast cancer in postmenopausal women. Adjuvant treatment of oestrogen receptor positive early invasive breast cancer in postmenopausal women following 2-3 years of tamoxifen. Advanced breast cancer in postmenopausal women which is oestrogen receptor positive or responsive to tamoxifen	AMBER Specialist initiation only; no formal shared care guideline is required at this stage.
Budesonide 100mcg per dose and 200mcg per dose metered dose inhalers CFC free (Pulmicort Inhaler CFC Free)	Licensed for the treatment of bronchial asthma.	GREEN Budesonide is a second line inhaled corticosteroid after beclometasone
Dabigatran etexilate (Pradaxa) capsules	An oral treatment licensed for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or elective total knee replacement surgery.	RED Unlikely to be prescribed from within ULHT due to preference for rivaroxaban.
Ethinylestradiol/ etonogestrel vaginal ring (NuvaRing)	Licensed as a form of contraception in women of fertile age	RED Approved for use by Sexual Health Services within restricted criteria only.
Exemestane (Aromasin) tablets	Licensed for: Adjuvant treatment of oestrogen receptor positive early breast cancer in postmenopausal women following 2-3 years of tamoxifen therapy. Advanced breast cancer in postmenopausal women in whom anti-oestrogen therapy has failed.	AMBER Specialist initiation only; no formal shared care guideline is required at this stage.
Fluticasone furoate nasal spray (Avamys)	Licensed for the treatment of allergic rhinitis in adults, adolescents and children over 6.	RED-RED
Grazax tablets	Licensed for grass pollen induced rhinitis and conjunctivitis diagnosed with a positive skin prick test and/or specific IgE test in adults and children aged 5 and over	RED-RED (Exceptional cases may be approved through the Local Exceptional Cases Committee)

Letrozole (Femara) tablets	Licensed for: Adjuvant treatment of oestrogen receptor positive early breast cancer in postmenopausal women. Early invasive breast cancer in postmenopausal women after standrard adjuvant tamoxifen therapy. Advanced breast cancer in postmenopausal women (including those in whom other anti-oestrogen therapy has failed) Pre-operative treatment in post menopausal women with localised hormone receptor positive breast cancer to allow subsequent breast conserving surgery	AMBER Specialist initiation only; no formal shared care guideline is required at this stage
Rivaroxaban (Xarelto) tablets	Licensed for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery**.**	RED N.B. Patients discharged from ULHT on rivaroxaban will have the complete course dispensed by the initiating hospital; GP prescribing is not recommended under any circumstances.

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 or tertiary care **only** and has **no role in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT/LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; in the coming months PACEF will be working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care**. Specialist initiation and shared care guidelines are not considered necessary.

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

LAUNCH OF NHS EVIDENCE

NHS Evidence is a new search engine designed specifically to enable health and social care staff to access high quality, relevant information in response to any query on any health related topic. All clinicians are urged to visit www.evidence.nhs.uk to try out this new search portal.

RAPID DRUG ASSESSMENT: FLUTICASONE FUROATE NASAL SPRAY (AVAMYS)

Fluticasone furoate is a new corticosteroid structurally related to fluticasone propionate. It is now available in a nasal spray formulation (Avamys) and is licensed for the treatment of allergic rhinitis in adults, adolescents and children over 6.
Efficacy data derives from 15 randomised controlled trials (RCTs). The main outcome for all studies was based on each patient's own assessment of the change in nasal symptoms compared to those experienced at the beginning of the study period.
Nine studies have been conducted in adults with seasonal rhinitis (SAR) and four in adults with perennial allergic rhinitis (PAR); a further two paediatric studies consider children with SAR and PAR respectively. Three studies in patients with SAR have active comparators: two studies compared fluticasone furoate and oral fexofenadine (180mg once daily) and a third compared fluticasone furoate with fluticasone propionate nasal spray (100mcg twice daily). The results from the active comparator trials showed fluticasone furoate to be non-inferior to fluticasone propionate with regards to symptom control; fluticasone furoate also demonstrated significantly greater reductions in symptom control compared to oral fexofenadine.
The study comparing fluticasone furoate to fluticasone propionate in SAR was conducted in Japan during the cedar pollen season; the results may not be transferable to a UK based population during the grass pollen season.

In vitro studies have shown fluticasone furoate to have a higher affinity for glucocorticoid receptors than fluticasone propionate and a higher selectivity than mometasone furoate. The manufacturer claims this higher affinity and selectivity may explain the prolonged duration of action. Fluticasone furoate is also delivered through a new nasal spray device which the manufacturer claims is easier and more comfortable for patients to use due to its shorter nozzle. Comparative studies against the fluticasone propionate device record patient preference for the Avamys device but are too subjective to be accepted as hard evidence. The Avamys device also delivers a consistent dose regardless of the force the patient applies and has a viewing window which allows patients to see exactly how much medication is left.

From the active comparator study in patients with PAR, the overall incidence of adverse events is comparable between fluticasone furoate and mometasone. The most commonly reported side effects were pharyngolaryngeal pain, epistaxis, nasopharyngitis and headache. There is a risk of growth retardation in children receiving prolonged treatment with nasal corticosteroids at licensed doses and the height of such children should be regularly monitored. In trials, a daily dose of fluticasone furoate of 110mcg was not associated with hypothalamic pituitary adrenal suppression in adults, adolescents or children.

A cost comparison reveals the following:

Drug	Daily dose range	Cost (£) per pack
Fluticasone furoate (Avamys) 27.5mcg/spray	**2 sprays/nostril once daily reduce to 1 spray per nostril once daily.**	**£6.44 (120 doses) per dose 5.4p /dose**

NHS Lincolnshire recommended products		
Beclometasone (generic)	2 sprays/nostril once daily reduce to 1 spray per nostril once daily.	£2.79 (200 doses) 1.4p/dose
Beclometasone (Beconase) 50mcg/spray	2 sprays/nostril twice daily reduce to 1 spray per nostril twice daily.	£2.19 (200 doses) 1.4p/dose
Budesonide 100mcg/spray	2 sprays/nostril once daily reduce to 1 spray per nostril once daily.	£5.90 (200 doses) 2.9p/dose
Mometasone (Nasonex Alcohol Free) 50mcg/spray	2 sprays/nostril once daily reduce to 1 spray per nostril once daily. Maximum dose 4 spray/nostril daily.	£7.83 (140 doses) 5.6p/dose
Alternative products		
Beclometasone (Nasobec) 50mcg/spray	2 sprays/nostril twice daily reduce to 1 spray per nostril twice daily.	£2.43 (200 doses) 1.2p/dose
Budesonide (Rhinocort Aqua) 64mcg/spray	2 sprays/nostril once daily reduce to 1 spray per nostril once daily.	£4.49 (120 doses) 3.7p/dose
Flunisolide (Syntaris) 25mcg/spray	2 sprays each nostril twice daily increasing to a maximum of three times daily. Reduce to minimum effective dose.	£5.05 (240 doses) 2.1p/dose
Fluticasone (Flixonase) 50mcg/spray	2 sprays/nostril once daily reduce to 1 spray per nostril once daily.	£11.23 (150 doses) 7.5p/dose
Triamcinolone (Nasacort) 55mcg/spray	2 sprays/nostril once daily reduce to 1 spray per nostril once daily.	£7.39 (120 doses) 6.2p/dose

PACEF Recommendation

Existing PACEF guidance recommends beclometasone aqueous nasal spray as the first line product of choice for the treatment of SAR; budesonide nasal spray or mometasone nasal spray (Nasonex Alcohol Free) are advocated second line. At this stage, no comparative data exists between fluticasone furoate nasal spray and beclometasone aqueous nasal spray. The new Avamys delivery device may offer some advantages over existing intranasal delivery systems, but comparative data is subjective and is only available comparing Avamys with the Flixonase device. Comparison of cost per dose for the various alternative formulations supports the continued use of beclometasone aqueous nasal spray first line. Fluticasone furoate nasal spray is comparably priced to the mometasone (Nasonex) product, but has demonstrated only equivalence in trials and has no long term safety data. At present PACEF remain unconvinced as to the advantages of fluticasone furoate over existing alternatives. The patent for fluticasone propionate expired in 2005, but additional patents on the delivery device have prevented a generic formulation of fluticasone propionate from appearing to date. A shift to a new branded formulation of a fluticasone based molecule could reduce the impact of potential generic savings if generic fluticasone propionate becomes available in the future. As a result of these concerns, fluticasone furoate nasal spray (Avamys) is designated RED-RED.

NEW DRUG ASSESSMENT APPEAL: ETHINYLESTRADIOL/ETONOGESTREL VAGINAL RING (NUVARING)

NuvaRing is a combined hormonal contraceptive vaginal ring containing ethinylestradiol (EE) and etonogestrel. Once inserted, the ring remains in place for three weeks releasing an average dose of 120mcg etonogestrel and 15mcg ethinylestradiol every 24 hours. Published trial evidence is limited to a number of studies investigating contraceptive efficacy and cycle control in comparison to a

narrow range of commonly prescribed oral contraceptives (Microgynon 30 and Yasmin). There are no published trials comparing the ring with alternative forms of contraception, although a Cochrane review from 2003 utilized existing data to conclude that the contraceptive effectiveness of the vaginal ring was comparable to combined oral contraception and the combined hormonal contraceptive patch. Comparative trials looking at cycle control show NuvaRing is linked to a lower incidence of late withdrawal bleeds and the establishment of more regular bleeding patterns than the combined oral contraceptive. The adverse effect profile and the list of contraindications are similar to those normally associated with combined hormonal contraception. Specifically, the use of the ring has been linked to local reactions such as vaginitis and increased vaginal discharge. NuvaRing has been available in the USA since 2002 and a number of European countries since 2003.

A cost comparison reveals that NuvaRing is considerably more expensive than combined oral contraception and even the combined hormonal contraceptive patch.

Drug	**Dose**	**Cost(£)/3mths**
NuvaRing (EE 15mcg, etonogestrel 120mcg)	**1 ring inserted for 3 weeks followed by ring free week.**	**£27.00**
Low strength (oral)		
Mercilon (EE 20mcg, desogestrol 150mcg)	1 tablet each day for 21 days followed by 7pill-free days.	£6.70
Low strength (transdermal)		
Evra (EE 20mcg, norelgestromin 150mcg)	1 patch each week for 3 weeks, followed by patch free week.	£16.26
Standard strength (oral)		
Microgynon 30/ Ovranette (EE 30mcg, levonorgesterol 150mcg)	1 tablet each day for 21 days followed by 7 pill-free days.	£2.99/£2.29
Yasmin (EE 30mcg, drospirenone 3mg)		£14.70

NuvaRing has a short shelf life of only 4 months at room temperature.

PACEF Recommendation:

PACEF have reviewed their original position on NuvaRing in response to an appeal. PACEF are convinced of the contraceptive efficacy, good cycle control and tolerability of NuvaRing, but remain concerned about the excessive cost in comparison to alternatives. As a result, NuvaRing is designated RED. It should only be prescribed from Sexual Health Services within the following criteria: (1) Patients with malabsorption, bowel disease or eating disorders causing vomiting; (2) Patients using antibiotics intermittently (e.g. cystic fibrosis, severe asthma, severe acne); (3) Patients with lactose intolerance; (4) Patients with mild hepatic disease; (5) Patients with a systemic disease necessitating lowest hormonal dose (e.g. diabetes); (6) Patients experiencing nausea with COCs; (7) Patients who have severe needle phobia and are unable to have injectable or implantable contraception; (8) Patients unable to swallow pills; (9) Patients with poor cycle control on oral contraceptives; (10) Patients with compliance problems with pills (e.g. those who have had an abortion while taking the pill, those with recurrent missed pills, those with a chaotic teenage lifestyle, shift workers and cabin crew). Subject to a successful trial within Sexual Health Services, the wider introduction of NuvaRing into primary care prescribing may be considered at a later date. In primary care, where the oral route is unsuitable due to hormonal related vomiting or nausea/vomiting related to other medical conditions or treatment, the combined hormonal contraceptive patch (Evra) is recommended as a preferred alternative.

NEW FORMULATION ASSESSMENT: BUDESONIDE CFC-FREE METERED DOSE INHALERS 100MCG AND 200MCG (PULMICORT INHALER CFC FREE)

AstraZeneca have now launched two strengths (100mcg and 200mcg per dose) of a chlorofluoro carbon (CFC) free budesonide metered dose inhaler (MDI) under the Pulmicort brand. Both strengths are licensed solely for asthma and are intended to replace the existing Pulmicort CFC containing MDIs.

PACEF Recommendations;
Both strengths of budesonide CFC-free MDIs (Pulmicort) are designated GREEN and switches are encouraged. Patients should be changed from their current Pulmicort CFC-containing inhaler to the same dose of Pulmicort CFC-free inhaler. This is straightforward for patients previously prescribed a Pulmicort CFC-containing MDI 200mcg per dose as a directly equivalent CFC-free version exists. Patients currently prescribed a Pulmicort LS inhaler (CFC-containing 50mcg per dose) should be transferred to the same dose of Pulmicort 100 CFC-free inhaler with the appropriate adjustment in number of doses (e.g. a patient currently prescribed Pulmicort LS inhaler 2 puffs twice daily should be changed to Pulmicort 100 CFC-free inhaler 1 puff twice daily). Patients prescribed Pulmicort LS inhaler 1 puff twice daily may be most appropriately changed to a beclometasone 50 inhaler 1 puff twice daily (beclometasone and budesonide can be considered to be equipotent). Where appropriate, for the same dose, it is more cost-effective to prescribe Pulmicort CFC-free 200mcg inhalers than Pulmicort CFC-free 100mcg inhalers. The CFC-free inhalers contain 120 doses compared to 200 doses for the CFC-containing inhalers and adjustments to the repeat prescribing interval will need to be made. Patients should be told that the CFC-free inhaler may feel different when in use (i.e. the puffs may feel less cold). The NebuChamber is the only spacer licensed for use with Pulmicort CFC-free inhalers. The NebuChamber is not prescribable, but is available at no charge from AstraZeneca representatives or direct from the company. Prescribers are reminded that budesonide constitutes a second line inhaled corticosteroid after beclometasone.

REVIEW: STANDARDISED GRASS POLLEN ALLERGEN FROM TIMOTHY GRASS (GRAZAX)

This feature is an update of the PACEF December 2007 review of Grazax that was originally published in the *PACE Bulletin,* Vol 2, No 1 (January 2008). All additions and amendments are highlighted in *italics.*

Grazax is the first oral vaccine licensed for the treatment of grass pollen induced rhinitis and conjunctivitis in patients with clinically relevant symptoms who have been diagnosed with a positive skin prick test and/or a specific Immunoglobulin E (IgE) test to grass pollen. *Since the last PACEF review the license has been extended from adults to include children of 5 years and older; it is not recommended in children under 5.* Grazax is formulated as a once daily fast melting sublingual tablet containing standardised allergen extract of Timothy grass pollen.

The GT-08 study, the most significant of the clinical trials, involved 634 pts aged between 18 and 65 with at least a two year history of significant grass pollen induced allergic rhinoconjunctivitis, a positive prick test to IgE and a FEV_1 higher than 70% of predicted value. Patients were randomised to either Grazax or placebo and self-scored their response in terms of symptom scores and use of rescue medication (such as desloratadine, budesonide nasal spray or oral prednisolone). The results

showed a statistically significant improvement in symptom scores and reduced use of rescue medication, although the rating scales used were based on the individual patient's evaluation of the severity of their symptoms and could be open to bias. The clinical significance of these findings remains uncertain. Second year data from GT-08 showed that Grazax significantly reduced the mean daily rhinoconjunctivitis symptom scores by 36% and the mean rhinoconjunctivitis medication score by 46% compared to placebo. Although long term effects are yet to be established, the results from the second year appear to suggest a continued reduction in the mean daily symptom and medication scores. *It must be stressed that both of these scores are patient measured, subjective and open to bias and that other studies, such as GT-02 and GT-07, have delivered less impressive results*.

An extension study to GT-08 is underway designed to determine the benefits of more prolonged Grazax treatment up to three years with a further two years follow-up. *Full data from the complete GT-08 trial is not expected to be published until Spring 2010, although limited access to third and fourth year data was granted to PACEF as part of this review.* For optimum results, Grazax should be taken daily for 16 weeks prior to the grass pollen season (in the UK normally late May to August) and continuously thereafter for a total of three years; some efficacy may be obtained if taken 2 to 3 months before the season starts. There is a high incidence of local oral reactions following administration, although, in general, the product appears to be well tolerated. There have been no reports of anaphylaxis, although angioedema and bronchospasm may occur in less than 1% of patients.

A cost comparison reveals the high cost of Grazax in comparison to other treatments:

Drug	**Daily dose range**	**Cost (£)pa**
Grazax tabs	**Once daily**	**£821.25**
Loratadine tabs	10mg daily	£15.57
Cetirizine tabs	10mg daily	£11.80
Beclometasone nasal spray	1 spray each nostril twice daily	£34.56
Sodium cromoglicate 2% eye drops	1 drop each eye four times a day	£25.61
Triamcinolone 40mg/ml	Single dose	£1.70
Pollinex	Course s/c injections	£320.00

Grasses and rye or tree pollen extract (Pollinex) subcutaneous therapy provides a possible alternative to Grazax, although there is an associated need for frequent clinic visits (normally for 8 to 16 weeks) and a greater risk of anaphylactic reactions during treatment. In addition, Grazax contains allergens to only one type of grass and therefore will not be suitable for other grass and tree pollen allergies, whereas Pollinex contains grass and rye pollens; there is also a separate Pollinex formulation containing tree pollen allergens.

The Scottish Medicines Consortium (SMC) review of Grazax concluded that whilst modest clinical benefit was shown, particularly by the GT-08 Study, the economic case was yet to be made. From economic data presented to the SMC by the manufacturer, the Cost per Quality Adjusted Life Year (QALY) for continued use compared to symptomatic treatment was calculated as £13,693; similarly the Cost per QALY for seasonal use compared to symptomatic treatment was £22,597. This raises serious questions regarding the lack of cost-effectiveness of Grazax, particularly when used seasonally. More positively, the SMC also compared the cost of continuous treatment with Grazax against a pre-seasonal course of subcutaneous immunotherapy (SCIT). The additional cost in Grazax treatment (£501 pa) was off set by a saving in the cost of drug administration of £772 compared to a course of SCIT

(based on the assumption that administration of SCIT requires six out-patient hospital appointments). This suggests that further work needs to be done to investigate the potential economic advantages of Grazax compared to SCIT in an out-patient setting. However, there is a lack of published studies comparing Grazax with symptomatic therapies or SCIT for hay fever; in the absence of such data it is difficult to recommend Grazax as a potential alternative to SCIT.

As part of this review, PACEF also considered the emerging evidence related to the use of Grazax in children. Grazax appears to be safe, efficacious and acceptable in the treatment of children with severe allergic rhinitis, although concerns over lack of comparative and long-term safety data remain and concerns over lack of cost-effectiveness are still to be addressed. It is more difficult to justify the use of Grazax in children with milder symptoms who require less medication and suffer fewer ill effects during the grass pollen season. Recent applications to the Lincolnshire Exceptional Cases Committee relating to Grazax have tended to focus on paediatric cases.

PACEF Recommendation:
PACEF remain unconvinced of the clinical and cost-effectiveness of Grazax in comparison to lower cost alternatives. As a result of this, Grazax remains RED-RED. It is recognized that there may be a limited role for the agent in patients who have not responded to optimal doses of conventional treatment for seasonal rhinitis and conjunctivitis and who are deemed unsuitable for subcutaneous therapy. Such patients must have a positive skin prick test or IgE test for grass pollen, specifically Timothy grass. In these circumstances, a specialist wishing to initiate therapy will need to first gain approval from the Local Exceptional Cases Committee (LECC). If the LECC approve Grazax for use in a specific patient this will be subject to specialist initiation and appropriate shared care arrangements.

References

1. Scottish Medicines Consortium (SMC) Re-Submission Standardised allergen extract of grass pollen from Timothy (phleum pratense) 75,000 SQ-T per oral lyophilisate (Grazax) 367/07 December 2007.
2. *Drug and Therapeutics Bulletin* February 2008. Grazax for hay fever? Vol 46 No 2 9-10.
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NEW TRIALS IN BRIEF: MAY 2009

Hypoglycaemic episodes and possible risk of dementia: *JAMA* 2009; 301: 1565-72

This cohort study of people with type 2 diabetes mellitus found an association between severe episodes of hypoglycaemia (requiring hospitalisation or visit to an emergency medical facility) and risk of dementia. It included 16,667 people in California (mean age 65 yrs). Cohort members with no prior diagnoses of dementia, cognitive impairment or general memory complaints on 1st January 2003 were followed up for a dementia diagnosis until 15th January 2007. The absolute increase in the risk of dementia was 2.39% per year of follow up for patients with a history of severe hypoglycaemia compared with patients with no history of this. The risk of

dementia was, on average, twice as likely in patients with three or more episodes of severe hypoglycaemia compared with those with no history of hypoglycaemia.

Reference: Whitmer RA et al. 'Hypoglycaemic episodes and risk of dementia in older patients with type 2 diabetes mellitus'. *JAMA* 2009; 301: 1565-72.

Naftidrofuryl and intermittent claudication: *BMJ* 2009;338: b603.

This is a meta-analysis of individual patient data taken from double blind randomised controlled trials (RCTs) involving patients with intermittent claudication receiving either naftidrofuryl or placebo; pain-free walking distance was taken as the primary outcome. A relative improvement in pain-free walking distance was demonstrated with naftidrofuryl compared with placebo. The number needed to treat (NNT) for relief of symptoms during 6 months of treatment was 4.48.

Reference: De Backer T et al. 'Naftidrofuryl for intermittent claudication: meta-analysis based on individual patient data'. *BMJ* 2009;338: b603.

NICE TECHNOLOGY APPRAISAL 170: *RIVAROXABAN FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER TOTAL HIP OR KNEE REPLACEMENT IN ADULTS* (APRIL 2009)

The key recommendation is as follows:

- Rivaroxaban (Xarelto), within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective total hip replacement surgery or elective total knee replacement surgery.

PACEF Recommendations:
Both rivaroxaban (Xarelto) and dabigatran etexilate (Pradaxa) have now been appraised and approved for use by NICE. As reported in *PACE Bulletin* Vol 3 No 1 (January 2009), ULHT Drug and Therapeutics Committee have undertaken a comparative assessment of both rivaroxaban and dabigatran etexilate. Following a detailed review of the data, they identified superior performance to enoxaparin in the rivaroxaban trials, whereas the dabigatran trials showed non-inferiority to the enoxaparin comparator. As a result of this, ULHT DTC have decided to recommended rivaroxaban as the treatment of choice within ULHT for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. PACEF have reviewed the same data and have ratified this decision. As a result if this, rivaroxaban (Xarelto) is designated RED. Dabigatran etexilate (Pradaxa) remains RED, but is unlikely to be used within ULHT due to the preference for rivaroxaban. Both drugs are for hospital prescribing only; patients discharged on either drug will have the complete course dispensed by the initiating hospital; GP prescribing is not recommended under any circumstances.

NICE CLINICAL GUIDELINE 80: *EARLY AND LOCALLY ADVANCED BREAST CANCER* (FEBRUARY 2009)

The key recommendations are as follows:

Pre-operative assessment of the breast

- Offer **magnetic resonance imaging (MRI) of the breast** to patients with invasive breast cancer: (1) if there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment; (2) if breast density precludes accurate mammographic assessment; (3) to assess tumour size if breast conserving surgery is being considered.
- Routine MRI of the breast is not recommended for patients with biopsy-proven breast cancer or ductal carcinoma in situ (DCIS).

Staging of the axilla

- Pretreatment **ultrasound evaluation of the axilla** should be performed for all patients being investigated for early invasive breast cancer; if abnormal lymph nodes are identified, ultrasound guided needle sampling should be offered.

Surgery to the axilla

- Minimal surgery, rather than lymph node clearance, should be performed to **stage the axilla** for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. Sentinel lymph node biopsy is the preferred technique.

Breast reconstruction

- Discuss immediate **breast reconstruction** with all patients who are being advised to have a mastectomy. Offer mastectomy where significant co-morbidity or (the need for) adjuvant therapy may preclude this option. All appropriate breast reconstruction options should be offered and discussed with patients.

Primary systemic therapy

- **Treat patients with early invasive breast cancer, irrespective of age, with surgery** and appropriate systemic therapy, rather than endocrine therapy alone, unless significant co-morbidity precludes surgery.
- Discuss with the patient the increased risk of local recurrence with breast conserving surgery and radiotherapy (RT) rather than mastectomy after systemic therapy.

Postoperative assessment

- For all patients with early invasive breast cancer: (1) use standardised and qualitatively assured methodologies to assess ER and HER2 status; (2) assess ER status using immunohistochemistry and report the result quantitatively; (3) ensure results of ER and HER2 status are available and recorded at the MDT meeting.
- Do not routinely assess progesterone receptor status.

Adjuvant therapy planning

- Start **adjuvant chemotherapy or radiotherapy** as soon as clinically possible and within 31 days of completion of surgery in patients with early breast cancer having these treatments.

Aromatase inhibitors

- Post-menopausal women with oestrogen receptor-positive early invasive breast cancer who are not considered to be at 'low risk' should be offered an **aromatase inhibitor (AI)**, either anastrozole or letrozole, as their initial adjuvant therapy. Offer tamoxifen if an aromatase inhibitor is contra-indicated or not tolerated. Low risk is defined as those in excellent or good prognostic health groups in the Nottingham Prognostic Index (NPI) who have 10-year

predictive survivals of 96% and 93% respectively; they would also have similar predictions using Adjuvant! Online.

- For more detailed explication of NICE recommendations on adjuvant therapy see table below:

Adjuvant therapy

Endocrine therapy	
ER-positive early invasive breast cancer, premenopausal women	Do not offer ovarian ablation/suppression to women having tamoxifen and chemotherapy. Offer ovarian ablation/suppression in addition to tamoxifen to women who have been offered chemotherapy but chosen not to have it.
ER-positive early invasive breast cancer, postmenopausal women who are not at low risk	Offer AI, either anastrozole or letrozole, as initial adjuvant therapy. Offer tamoxifen if AI is not tolerated or contraindicated
ER-positive early invasive breast cancer, postmenopausal women who are not at low risk and who have been treated with tamoxifen for 2-3 years	Offer AI, either anastrozole or exemestane, instead of tamoxifen.
ER-positive lymph-node positive early invasive breast cancer, postmenopausal women who have been treated with tamoxifen for 5 years	Offer additional treatment with the AI letrozole for 2-3 years.
ER-positive early invasive breast cancer, postmenopausal women	The AIs anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for adjuvant treatment
ER-positive early invasive breast cancer	Discuss risks and benefits of each treatment option. Consider previous treatment with tamoxifen, licensed indications and side effects of individual drugs and assessed risk of recurrence.
DCIS after breast conserving surgery	Do not offer tamoxifen

- The licensed indications and contra-indications of the three AIs are as follows:

Drug	**Licensed Indications**	**Contra-indications**
Anastrozole (Arimidex)	Adjuvant treatment of oestrogen receptor positive early invasive breast cancer in postmenopausal women. Adjuvant treatment of oestrogen receptor positive early invasive breast cancer in postmenopausal women following 2-3 years of tamoxifen. Advanced breast cancer in postmenopausal women which is oestrogen receptor positive or responsive to tamoxifen	Pregnancy and breast-feeding; moderate or severe hepatic disease; moderate or severe renal impairment; not for premenopausal women
Exemestane (Aromasin)	Adjuvant treatment of oestrogen receptor positive early breast cancer in postmenopausal women following 2-3 years of tamoxifen therapy. Advanced breast cancer in postmenopausal women in whom anti-oestrogen therapy has failed.	Pregnancy and breast-feeding; not for premenopausal women
Letrozole (Femara)	Adjuvant treatment of oestrogen receptor positive early breast cancer in postmenopausal women. Early invasive breast cancer in postmenopausal women after standrard adjuvant tamoxifen therapy. Advanced breast cancer in	Pregnancy and breast-feeding; severe hepatic impairment; not for premenopausal women

	postmenopausal women (including those in whom other anti-oestrogen therapy has failed) Pre-operative treatment in post menopausal women with localised hormone receptor positive breast cancer to allow subsequent breast conserving surgery	

- Comparative costs are as follows:

Drug	Dose	Cost (28 days)
Anastrazole tablets 1mg (Arimidex)	1mg daily	£68.56
Exemestane tablets 25mg	25mg daily	£82.88
Letrozole tablets 2.5mg (Femara)	2.5mg daily	£66.50

Assessment of bone loss

- Patients with early invasive breast cancer should have a **baseline dual energy X-Ray absorptiometry (DEXA) scan** to assess bone mineral density (BMD) if they: (1) are starting adjuvant aromatase inhibitor treatment; (2) have treatment-induced menopause; (3) are starting ovarian ablation/suppression therapy.
- Do not offer DEXA to patients with early invasive breast cancer who are receiving tamoxifen alone, regardless of pre-treatment menopausal status.
- Bisphosphonates may be indicated for patients identified by algorithms 1 and 2 in 'Guidance for the management of breast cancer treatment-induced bone loss'.

Follow-up imaging

- Offer annual mammography to all patients with early breast cancer, including ductal carcinoma in situ, until they enter the NHS Breast Screening Programme. Patients diagnosed with early breast cancer who are already eligible for screening should have annual mammography for 5 years.

Clinical follow-up

- Patients treated for breast cancer should have an agreed, written care plan.

Menopausal symptoms

- Early menopause and menopausal symptoms are associated with breast cancer treatment.
- HRT should be discontinued in women diagnosed with breast cancer.
- HRT should not be used routinely in women with menopausal symptoms and a history of breast cancer.
- HRT may, in exceptional cases, be given to women with early breast cancer who have severe menopausal symptoms, as long as the woman has been fully informed about the risks.
- SSRI antidepressants (paroxetine and fluoxetine) may be used to relieve menopausal symptoms, particularly hot flushes, but not in women taking tamoxifen (NB Paroxetine and fluoxetine are unlicensed for this indication)
- Clonidine, venlafaxine and gabapentin should only be used to treat hot flushes after the woman has been fully informed of the significant side effects (all unlicensed).
- Tibolone, progestogens, soy (isoflavone), red clover, black cohosh, vitamin E and magnetic devices are not recommended to treat menopausal symptoms.

PACEF Recommendation:
Prescribers are reminded that all three aromatase inhibitors (anastrazole, exemestane and letrozole) are designated AMBER. These drugs should only be initiated by a specialist, but do not, at present, require a formal shared care guideline.

NICE CLINICAL GUIDELINE 81: *ADVANCED BREAST CANCER* (FEBRUARY 2009)

The key recommendations are as follows:

Diagnosis and assessment

- Positron emission tomography fused with computed tomography (PET-CT) should only be used to make a new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease.
- Assess oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status at the time of disease recurrence if receptor status was not assessed at the time of initial diagnosis. In the absence of tumour tissue from the primary tumour, and if feasible, obtain a biopsy of a metastasis to assess ER and HER2 status.

Systemic disease-modifying therapy

- Offer endocrine therapy as first-line treatment for the majority of patients with ER positive advanced breast cancer.
- Offer chemotherapy as first-line treatment for patients with ER-positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity.
- For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy following the completion of chemotherapy.
- For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence: (1) first-line – single agent docetaxel; (2) second-line – single agent vinorelbine or capecitabine; (3) third-line – single agent capecitabine or vinorelbine (whichever was not used second line).
- For patients who are receiving treatment with trastuzumab for advanced breast cancer, discontinue treatment with trastuzumab at the time of disease progression outside the central nervous system. Do not discontinue trastuzumab if disease progression is within the central nervous system alone.
- Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate

Endocrine therapy

- Offer an aromatase inhibitor (AI) (either non-steroidal or steroidal) to: postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy; postmenopausal women with ER-positive breast cancer previously treated with tamoxifen.

- Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen.
- Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression.
- Offer tamoxifen as the first line treatment for men with oestrogen receptor-positive advanced breast cancer.

Supportive care

- Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as diagnosis, commencement, during and at the end of treatment; at relapse; and when death is approaching).
- Continuity of care should be promoted through the nomination of a key worker for individual patients.

Advanced Breast Cancer Pathway

- Includes diagnosis and assessment, endocrine therapy (i.e. tamoxifen or aromatase inhibitors) and chemotherapy.
- Post-menopausal women with oestrogen receptor-positive advanced breast cancer should be offered an **aromatase inhibitor (AI)** as their initial adjuvant therapy.
- Tamoxifen has a role in pre or perimenopausal women with oestrogen receptor-positive advanced breast cancer.

Managing complications

- Emphasizes the importance of a breast cancer multidisciplinary team.

Lymphoedema

- Identify and treat underlying factors before starting lymphoedema therapy.
- Offer complex decongestant therapy (CDT) first line.
- Consider multi-layer lymphoedema bandaging (MLLB) for volume reduction before compression hosiery. Provide patients with at least 2 compression garments.

Uncontrolled local disease

- A wound care team should see patients with fungating tumours to plan a dressing regimen.
- A palliative care team should assess patients to plan a symptom management strategy and provide psychological support.

Bone metastases

- Consider bisphosphonates for patients newly diagnosed with bone metastases, to prevent skeletal-related events and reduce pain.
- The choice of bisphosphonates should be a local decision taking into account patient preference and limited to preparations licensed for this indication. The licensed preparations are: disodium pamidronate IV infusion (Aredia), ibandronic acid (Bondronat), sodium clodronate (Bonefos) and zoledronic acid infusion (Zometa).
- Use external beam radiotherapy (RT) in a single fraction of 8Gy to treat patients with bone metastases and pain.

Brain metastases

- Offer surgery followed by whole brain RT to patients who have a single or small number of potentially resectable brain metastases, a good performance status and who have no or well controlled other metastatic disease.
- Offer whole brain RT to patients for whom surgery is not appropriate, unless they have a very poor prognosis.

SHARED CARE GUIDELINES: *ACETYLCHOLINESTERASE INHIBITORS FOR THE TREATMENT OF MODERATELY SEVERE ALZHEIMER'S DISEASE*

PACEF have approved a shared care guideline entitled *Acetylcholinesterase inhibitors for the treatment of moderately severe Alzheimer's disease*.

Copies are available from Cathy Johnson, Interface Lead Pharmacist at cathy.johnson@lpct.nhs.uk

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA): SAFETY UPDATE (MAY 2009)

Aliskiren: Risk of Angioedema and Renal Dysfunction

- Aliskiren (Rasilez) is the first of a potentially new class of oral antihypertensive agents known as renin inhibitors. It is licensed for the treatment of essential hypertension and can be used either as monotherapy or in combination with other antihypertensive agents.
- The MHRA have now issued advice to healthcare professionals following the emergence of safety concerns.

Advice for healthcare professionals:

- Aliskiren should not be used for the management of hypertension in patients who have previously experienced angioedema when using it.
- Patients should be advised to stop aliskiren and seek immediate medical advice if they develop the symptoms of angioedema (e.g. swelling of the face, eyes, lips or tongue (or both), hands and feet, or difficulty breathing or swallowing).
- Extreme caution is required if aliskiren is used in patients with renal artery stenosis or conditions predisposing to kidney dysfunction (e.g. hypovolaemia, heart disease, liver disease or kidney disease) because of a risk of acute renal failure. Discontinue aliskiren promptly if any signs of renal failure occur.
- NSAIDs may reduce the antihypertensive effect of aliskiren.
- Elderly patients or patients with compromised renal function may be at risk of further deterioration of renal function if NSAIDs and aliskiren are used together.

PACEF Recommendation:
Most of the published data relating to aliskiren is from short-term trials that reveal nothing about long-term efficacy, long-term safety, cost-effectiveness or impact on cardiovascular outcomes. Advice recently issued by the MHRA highlights emerging safety concerns. Nonetheless, aliskiren may have a role in patients intolerant to or unresponsive to standard therapies. The number of unanswered questions and the prohibitive comparative cost necessitates that aliskiren should be confined to patients with multiple intolerance to other antihypertensive medications or resistant hypertension. PACEF designation: AMBER. Aliskiren is only appropriate in a small number of carefully selected patients on the advice of a specialist. GPs can initiate following specialist recommendation; no shared care guideline is required at present.

ACE Inhibitors and Angiotensin II Receptor Antagonists: Recommendations on use during breast feeding

- Angiotensin II is essential for normal kidney development. The use of ACEIs and AIIRAs is not recommended at any stage of pregnancy unless absolutely necessary.
- ACEIs have a small molecular size and so their transfer to breast milk is possible.

Advice for healthcare professionals:

ACE inhibitors (ACEIs)

- Captopril, enalapril or quinapril: use in breastfeeding is not recommended in the first few weeks after delivery because of the possibility of profound neonatal hypotension; preterm babies may be at particular risk. Use may be considered when the infant is older if an ACEI is necessary for the mother; careful follow-up of the infant for possible signs of hypotension is recommended.
- Ramipril, lisinopril, fosinopril, trandolapril, moexipril or perindopril: use in breastfeeding is not recommended. Alternative treatments with more established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm baby

All Angiotensin II receptor antagonists (AIIRAs)

- Use in breastfeeding mothers is not recommended. Alternative treatments with more established safety profiles during breastfeeding are preferable, especially while nursing a newborn or preterm baby

Non-Steroidal Anti-Inflammatory Drugs: Renal failure and impairment

Advice for healthcare professionals:

- Patients at risk of renal impairment or renal failure (particularly elderly people) should avoid NSAIDs if possible. If NSAID treatment is absolutely necessary, use the lowest effective dose for the shortest possible duration. Renal function of such patients should be carefully monitored.
- When prescribing NSAIDs, consider other concomitant disease states, conditions or medicines that may precipitate reduced renal function.

New advice on oral salicylate gels for those younger than 16 years

The MHRA review of oral salicylate gels was triggered by the publication of a case report of suspected Reye's syndrome in a 20 month old child that had been using a dental gel containing choline salicylate. The review has resulted in the Commission on Human Medicines contraindicating oral salicylate gels in those younger than 16. The products affected are: Bonjela Gel, Bonjela Cool Gel, Dinnefords Teejel Gel and Pyralvex.

Advice for healthcare professionals:

- Advise parents and patients that those younger than 16 should use alternative treatments or products. There are several dental gels available which contain a local anaesthetic/mild antiseptic (e.g. Anbesol Teething Gel, Bonjela Teething Gel, Calgel Teething Gel, Dentinox Teething Gel).
- For infant teething, gentle pressure with something cool such as a chilled teething ring may help.

- For pain associated with orthodontic devices, salt water mouthwashes are recommended for sore areas. For discomfort arising from tooth movement, a paracetamol-based painkiller is recommended.

Fortodol: Risk of serious liver damage

The Food Standards Agency (FSA) has issued a warning about the food supplement Fortodol. Fortodol is sold in the UK and on the internet claiming benefits relating to relief of arthritis, muscle pains and headaches. According to the FSA, the product may contain nimesulide (an anti-inflammatory drug associated with a risk of liver damage). Any person currently using this product should be advised to stop immediately.

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