NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 6; Number 4 **February 2012**

What's new this month?

- **Both tapentadol immediate release tablets (Palexia) and tapentadol prolonged release tablets (Palexia SR) have been designated RED-RED (see page 3).**
- **Atorvastatin chewable tablets (Lipitor) are designated RED-RED, although it is recognized that there are exceptional circumstances where they may have a limited role (i.e. hypercholesterolaemia in children over 10 years and patients with swallowing difficulties unable to cope with lower cost alternatives)(see page 4).**
- **In view of the supply problems with ketoprofen 2.5% gel, alternative topical NSAIDs are reviewed and lower cost alternatives identified. These include: generic ibuprofen 5% gel (100g £4.95), ibuprofen 5% gel (Ibugel) (100g £4.87), ibuprofen 5% gel (Fenbid) (100g £1.50), ibuprofen gel 10% (Fenbid) (100g £4.00) and piroxicam gel 0.5% (112g £3.40). Of these, ibuprofen 5% gel (Fenbid) emerges as the lowest cost, but only if supplied in the 100g tube (i.e. not 2 x 50g) (see page 4).**
- **Key patent expiries for 2012/13 are reviewed (see page 6). The impact of the atorvastatin patent expiry and the need for associated review of rosuvastatin prescribing is considered in detail (see page 8)**
- **Safety concerns with dabigatran (Pradaxa) are reviewed (see page 10).**

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: FEBRUARY 2012 UPDATE

Drug	Indication(s)	Traffic Light Status
Atorvastatin chewable tablets (Lipitor)	As an adjunct to diet in primary hypercholesterolaemia or mixed dyslipidaemia when response to diet and other non-pharmacological	RED-RED Subject to infrequent exceptions.

	measures is inadequate. As an adjunct to diet in homozygous familial hypercholesterolaemia. Primary prevention of cardiovascular events in high-risk patients as an adjunct to the correction of other risk factors.	
Dabigatran etexilate capsules (Pradaxa)	Licensed for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and one or more of the following: • previous stroke, transient ischaemic attack or systemic embolism. • LVEF <40%. • symptomatic heart failure (≥ NYHA class II). • ≥ 75 years. • ≥ 65 years with diabetes, coronary artery disease or hypertension (110mg and 150mg capsules only).	RED-RED Subject to review once NICE publish their forthcoming TA.
Dabigatran etexilate capsules (Pradaxa)	Licensed for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip or knee replacement surgery	RED Full course provided from initiating hospital (not approved for use within ULHT).
Panitumumab intravenous infusion (Vectibix)	Licensed for the treatment of EGFR-expressing metastatic colorectal carcinoma, with non-mutated KRAS after failure of fluoropyrimidine, oxaliplatin and irinotecan containing regimens	RED-RED
Ranibizumab intravitreal injection (Lucentis)	Licensed for neovascular (wet) age-related macular degeneration.	RED
Ranibizumab intravitreal injection (Lucentis)	Licensed for the treatment of visual impairment due to diabetic macular oedema or macular oedema secondary to retinal vein occlusion.	RED-RED
Tapentadol immediate-release tablets (Palexia)	Licensed for the relief of moderate to severe acute pain in adults.	RED-RED
Tapentadol prolonged-release tablets (Palexia SR)	Licensed for the management of severe chronic pain in adults.	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.**

NEW DRUG ASSESSMENT: *TAPENTADOL IMMEDIATE RELEASE TABLETS (PALEXIA) AND TAPENTADOL PROLONGED RELEASE TABLETS (PALEXIA SR)*

Tapentadol is an opioid analgesic combining two mechanisms of action: mu-opioid receptor agonism and noradrenaline reuptake inhibition. The prolonged-release tablets (Palexia SR) are licensed for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics. The immediate-release tablets (Palexia) are licensed for the relief of moderate to severe acute pain in adults.

The efficacy of tapentadol prolonged-release has been assessed in osteoarthritis, low-back and diabetic neuropathic pain. Tapentadol is significantly more effective than placebo in reducing average pain intensity, and non-inferior to oxycodone controlled-release. Tapentadol has not been compared with opioid analgesics other than oxycodone and it has not been studied in cancer pain. The incidence of gastro-intestinal adverse effects is less common with tapentadol than with oxycodone.

The efficacy of tapentadol immediate-release has been assessed in the management of acute pain associated with bunionectomy and end-stage joint disease. Tapentadol is significantly more effective than placebo in reducing average pain intensity and 50 and 75mg doses are non-inferior to oxycodone 10mg.

Tapentadol prolonged-release is the same cost as oxycodone controlled-release in primary care; immediate-release is slightly more expensive than oxycodone.

PACEF Recommendation:
PACEF were concerned about the lack of comparative data between tapentadol and lower cost opioid alternatives such as modified release morphine. It was acknowledged that the drug emerged as non-inferior to oxycodone in trials, better tolerated and at a similar cost, but oxycodone is a high-cost intervention in comparison to alternatives. As a result of this both tapentadol immediate release tablets (Palexia) and prolonged release tablets (Palexia SR) were designated RED-RED.

NEW FORMULATION ASSESSMENT: *ATORVASTATIN CHEWABLE TABLETS (LIPITOR)*

Pfizer have recently launched a chewable atorvastatin tablet licensed identically to the established standard atorvastatin tablet. PACEF evaluated this product both in terms of its paediatric role and as an alternative for patients who experience difficulties taking statins in tablet form due to swallowing difficulties. Atorvastatin is licensed for the treatment of hypercholesterolaemia in children over 10 years, although this role is extremely limited and largely subject to advice from specialist tertiary centres. Similarly, the prescribing of licensed and unlicensed statin liquid formulations in Lincolnshire is low, although high-cost liquid specials remain a problem and can result in disproportionately high statin prescribing costs around individual patients. Currently, chewable atorvastatin is priced slightly higher than the standard atorvastatin tablet formulation:

Drug	Daily dose range	Cost (£) (28 days)
Atorvastatin chewable tablets (Lipitor)	10mg	£13.80
	20mg	£26.40
Atorvastatin tablets (Lipitor)	10mg	£13.00
	20mg	£24.64
	40mg	£24.64
	80mg	£28.21

PACEF Recommendations:
In view of the forthcoming atorvastatin (Lipitor) patent expiry in May 2012, PACEF are reluctant to endorse the use of this new chewable formulation which will reduce potential generic savings if it becomes significantly established. The paediatric role in children over 10 is extremely limited and likely to be led by specialist advice. With adult patients genuinely experiencing swallowing difficulties, standard advice published in *PACE Bulletin*, Vol 4 No 17 (November 2010) applies. Standard atorvastatin tablets can be crushed or dispersed slowly in 10mls of water; alternatively, simvastatin tablets can be dispersed in water or crushed. Atorvastatin liquid specials are available, but are not licensed for purpose and are prohibitively expensive. In accordance with MHRA advice, use of a licensed product (i.e. simvastatin or atorvastatin tablets) in an unlicensed way (i.e. dispersed in water or crushed) is always preferable to use of an unlicensed product. Atorvastatin chewable tablets (Lipitor) are designated RED-RED, although it is recognized that there are exceptional circumstances where they may have a limited role (i.e. hypercholesterolaemia in children over 10 years and patients with swallowing difficulties unable to cope with lower cost alternatives).

REVIEW: *TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)*

In NICE Clinical Guideline 59: *Osteoarthritis – the care and management of osteoarthritis in adults* (February 2008), NICE recommend that the pharmaceutical treatment of OA should commence with relatively safe options such as paracetamol and/or topical non-steroidal anti-inflammatory drugs (NSAIDs). Topical NSAIDs are particularly recommended in knee or hand OA (see *PACE Bulletin* Vol 2 No 7 (May 2008)).

Long standing supply problems affecting the availability of generic ketoprofen 2.5% gel (a preferred first line option) have necessitated a review of the comparative costs of alternative topical NSAIDs. Preferred lower-cost first line options are highlighted in bold.

Topical NSAID	Cost (£)	Pack size (g)
	3.99	30
	2.85	50
Ketoprofen Gel 2.5% (supply difficulties)	**3.73**	**100**
Oruvail Gel 2.5%	6.84	100
	3.06	50
Powergel 2.5%	5.89	100
	2.10	30
	2.78	50
Ibuprofen Gel 5% (generic)	**4.95**	**100**
Ibugel 5%	**4.87**	**100**
Fenbid Gel 5%	2.10	30

	2.65	50
	1.50	**100**
Ibuprofen Gel 10%	5.79	100
	2.65	30
Fenbid Gel 10%	**4.00**	**100**
Ibugel Forte 10%	5.79	100
	2.62	60
Piroxicam Gel 0.5%	**3.40**	**112**
	6.00	60
Feldene Gel 0.5%	9.41	112
Diclofenac Gel 1%	7.00	100
	2.26	30
Felbinac Gel 3%	8.03	100

PACEF Recommendations:
Topical NSAIDs of low acquisition cost should be prescribed first line. Lower cost topical NSAIDs currently available include: generic ibuprofen 5% gel (100g £4.95), ibuprofen 5% gel (Ibugel) (100g £4.87), ibuprofen 5% gel (Fenbid) (100g £1.50), ibuprofen gel 10% (Fenbid) (100g £4.00) and piroxicam gel 0.5% (112g £3.40). Of these, ibuprofen 5% gel (Fenbid) emerges as the lowest cost, but only if supplied in the 100g tube (i.e. not 2 x 50g).
The use of premium price products such as ketoprofen gel 2.5% (Oruvail/ Powergel), ibuprofen gel 10% (Ibugel Forte), piroxicam gel 0.5% (Feldene), felbinac gel 3% and foam 3.17% (Traxam) and diclofenac gel (Voltarol Emulgel) should be avoided where possible. PACEF are currently working with ULH Drug and Therapeutics Committee to reduce the initiation of diclofenac gel (Voltarol Emulgel) within United Lincolnshire Hospitals.

NICE TECHNOLOGY APPRAISAL 237: *RANIBIZUMAB FOR THE TREATMENT OF DIABETIC MACULAR OEDEMA* (NOVEMBER 2011)

Key Recommendation

Ranibizumab is not recommended for the treatment of visual impairment due to diabetic macular oedema. People currently receiving ranibizumab for the treatment of visual impairment due to diabetic macular oedema should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

PACEF Recommendation:
Ranibizumab intravitreal injection (Lucentis) has already been approved by NICE for the treatment of wet age related macular degeneration subject to criteria and has been designated RED for this indication by PACEF. Following the publication of NICE TA237, ranibizumab is designated RED-RED for the treatment of diabetic macular oedema.

NICE TECHNOLOGY APPRAISAL 240: *PANITUMUMAB IN COMBINATION WITH CHEMOTHERAPY FOR THE TREATMENT OF METASTATIC COLORECTAL CANCER* (DECEMBER 2011)

Key Recommendation

NICE is unable to recommend the use in the NHS of panitumumab in combination with chemotherapy for the treatment of metastatic colorectal cancer because no

evidence submission was received from the manufacturer or sponsor of the technology. This appraisal relates to the treatment of wild-type KRAS metastatic colorectal cancer for first-line treatment in combination with FOLFOX, and for second-line treatment in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).

PACEF Recommendation:
Panitumumab intravenous infusion (Vectibix) in combination with chemotherapy is designated RED-RED for the treatment of metastatic colorectal cancer.

KEY PATENT EXPIRIES 2012/13

Many prominent brand name pharmaceuticals are due to go off-patent within the next 12 months. The most widely anticipated of these is atorvastatin (Lipitor) in May 2012 (discussed in some detail later in the *Bulletin*). The table below highlights the most important patent expiries and their implications for primary care.

Patent Expiries 2012/13

	Drug	**Implications**
September 2011	Olanzapine	Olanzapine generics are currently available, but the NHS reimbursement price is yet to fall significantly. Prescribers should ensure that all scripts are genericized and that the use of line extensions such as olanzapine orodispersible tablets (Zyprexa Velotab) is reviewed.
November 2011	Valsartan	Switches away from the longer patent life A2RAs (olmesartan and telmisartan) are in process in many practices. Many of the remaining A2RAs are likely to become available as low cost generics in the coming 12 months. NICE now recommend an ACEI or a low cost A2RA as first line treatment of choice in people under 55 with hypertension (see *PACE Bulletin* Vol 6 No 1 (January 2012). At present, losartan is the only low cost A2RA available but this is set to change in the coming months. Prescribers who were reluctant to support therapeutic switching to losartan will be asked to reconsider once a wider range of generic A2RAs becomes available.

	Drug	Implications
January 2012	Latanoprost eye preparations	PACEF guidance on the treatment of glaucoma will be reviewed in early 2012 to address the implications for therapy of low cost latanoprost eye preparations in comparison to higher cost branded preparations (bimatoprost, tafluprost and travoprost). Generic latanoprost/timolol eye preparations are also likely to become available later in 2012.
January 2012	Galantamine	NICE recommend all three acetylcholinesterase (AChE) inhibitors, donepezil, galantamine and rivastigmine, as options for the management of mild to moderate

		Alzheimer's disease. However, they emphasise the importance of starting therapy with the AChE inhibitor of lowest acquisition cost. At present, all three medicines are broadly comparable in price; patent expiry and generic availability may change this and will be kept under review.
February 2012	Donepezil	See galantamine section.
February 2012	Mometasone furoate	The impact of this on the price of the range of products containing mometasone in relation to alternatives remains to be seen.
March 2012	Zolmitriptan Naratriptan	This is likely to affect preferred first line treatment choices for migraine. PACEF will review later in the year once the implications of generic price reductions become fully apparent.
March 2012	Quetiapine	Another key atypical antipsychotic patent expiry that should contribute to significant reductions in prescribing costs in mental health in 2012/13. Guidance around the use of Seroquel XL will be reviewed by PACEF in preparation.
April 2012	Eprosartan mesylate Candesartan	See valsartan section. Many practices in Lincolnshire favour candesartan and will make significant savings from this patent expiry. Therapeutic switching from telmisartan/olmesartan to candesartan is likely to be an option in some practices.
May 2012	Atorvastatin calcium lactate	A long awaited patent expiry that should result in low cost generic atorvastatin by October 2012. Simvastatin 40mg will remain the first line drug of choice, but practices should ensure that atorvastatin becomes the preferred second line statin of choice (where simvastatin and pravastatin are either insufficiently effective or poorly tolerated). Practices currently prescribing rosuvastatin in this role will need to review their practice. Product switching away from rosuvastatin will remain a priority in 2012/13 in preparation for this patent expiry. New initiations of rosuvastatin will be strongly discouraged (see below).
July 2012	Rivastigmine	See galantamine section.
August 2012	Irbesartan	See valsartan section.
August 2012	Montelukast sodium	
September 2012	Tolterodine tartrate	Low cost generic tolterodine is likely to significantly reduce treatment costs in the area of urinary incontinence. Guidance on the treatment of over active bladder is under review with urologists. The role of tolterodine will be clarified and the future of line extensions such as Detrusitol XL considered. The place of higher cost alternatives such as fesoterodine (Toviaz) (currently RED-RED) is also part of this review.
September 2012	Ramipril plus felodipine	
November 2012	Rabeprazole	The final PPI patent expiry; most practices are already using generically available lower cost alternatives.
December 2012	Duloxetine	

February 2013	Clopidogrel hydrogen sulphate	Low cost generic clopidogrel salts are already widely prescribed.
March 2013	Dorzolamine plus timolol	PACEF guidance on the treatment of glaucoma will be reviewed in early 2012.

ATORVASTATIN PATENT EXPIRY AND THE FUTURE ROLE OF ROSUVASTATIN

The atorvastatin (Lipitor) patent is due to expire in May 2012 with generic versions expected to be available from wholesalers from the outset. It will take some time for the generic reimbursement price of atorvastatin to fall, but the interest from generic manufacturers and the likelihood of strong competition between different generic atorvastatin products is likely to drive prices down relatively quickly. As a result, it is expected that generic atorvastatin will move into Category M of the *Drug Tariff* very quickly with NHS reimbursement prices expected to begin to fall by October 2012. In preparation for this, PACEF have already endorsed atorvastatin as our preferred high-cost high-potency statin where lower cost generic statins are either insufficiently effective or poorly tolerated. In a best case scenario where atorvastatin prices fall to a level comparable with the current simvastatin 40mg generic price, the likely annual savings across Lincolnshire are £3.88M pa broken down between the Clinical Commissioning Groups as follows:

	Potential Annual Saving
Boston CCG	£358,000
East Lindsey CCG	£383,500
Lincolnshire SW CCG	£519,700
Lincolnshire West CCG	£1.08M
Skegness CCG	£657,400
South Holland CCG	£537,700
Welland CCG	£339,500
Lincolnshire	£3.88M

The speed and extent to which generic atorvastatin prices will fall remains to be seen; while the financial impact of the atorvastatin patent expiry will be significant, it is likely to be 2013/14 before the full impact is felt. Nonetheless, Lincolnshire CCGs supported by the Prescribing and Medicines Management Team will need to take action in the coming months to ensure that Lincolnshire maximises the potential impact of the savings linked to this patent expiry.

PACEF Recommendations:
Practices should continue to follow existing PACEF lipid modification guidance (see *PACE Bulletin* Vol 4 No 13 (August 2010). Simvastatin 40mg remains the first line drug of choice in both primary and secondary prevention of CVD. In secondary prevention of CVD where treatment to target is advocated (5mmol/l Total Cholesterol; 3mmlol/l LDL-C), atorvastatin is the second line statin of choice (where simvastatin and pravastatin are either insufficiently effective or poorly tolerated). In primary prevention of CVD a standard 'fire-and-forget' dose of simvastatin 40mg (or pravastatin 40mg if not tolerated) should be sufficient for most patients.

What about rosuvastatin (Crestor)?

Licensed indications, outcomes data and safety concerns

Rosuvastatin (Crestor) has a narrower range of licensed indications than most of the other statins. It is licensed for the treatment of hypercholesterolaemia (including

familial hypercholesterolemia) and for the prevention of cardiovascular events in patients at high risk of first cardiovascular event (primary prevention).It is not licensed for the secondary prevention of CVD, despite its widespread use for this indication. Until the publication of the JUPITER trial there was no published outcomes data available. The recently published SATURN study compared treatment with atorvastatin 80mg or rosuvastatin 40mg in people with CHD. Both groups saw a regression in atherosclerosis from baseline in about two-thirds of patients but there was no statistically significant difference between the two groups.

PACEF Recommendations:
Rosuvastatin (Crestor) is not licensed for the secondary prevention of CVD despite the fact that the majority of prescriptions written for rosuvastatin each year are for this indication. Safety concerns remain around the risk of muscle disorders and rhabdomyolysis at the higher doses and have been recently reiterated by the MHRA (see *PACE Bulletin*, Vol 6 No 3 (January 2012)). As a result of this, the prescribing of rosuvastatin is only justified if a patient with raised cholesterol does not respond adequately to maximal doses of other statins or if a patient cannot tolerate alternatives. Advice from local cardiologists is that a low dose of rosuvastatin (5mg) may be tolerated where intolerance to other statins has been proven to be a problem. Rosuvastatin should always be considered prior to introducing ezetimibe as it is comparable in cost, substantially more effective at lowering TC and LDL-C and has published outcomes data. Rosuvastatin (Crestor) remains under patent until 2018 and will become the only remaining high-cost, high-potency branded statin after May 2012. Prescribers are urged to review all patients currently taking rosuvastatin to ensure that: (1) rosuvastatin is not being inadvertently prescribed for primary prevention of CVD where simvastatin 40mg or pravastatin 40mg should be the dominant products; (2) the majority of patients prescribed rosuvastatin for secondary prevention of CVD are switched to simvastatin 40mg where this has never been tried or an equivalent dose of atorvastatin where a high-potency agent is clinically necessary. Patients who are intolerant to alternatives or who have failed to respond sufficiently to alternative statins can remain on rosuvastatin therapy, although this is envisaged to be far fewer patients than are currently treated with the drug.

Financial implications

We currently spend £1.9Mpa on rosuvastatin in Lincolnshire and £4.5Mpa in East Midlands as a whole. Almost half of the rosuvastatin prescribed in the whole of the East Midlands is in our county. The quarterly expenditure on rosuvastatin in each of the Lincolnshire CCGs is detailed below (September 2011 Qtr):

	Quarterly Expenditure (September 2011 Qtr)
Boston CCG	£43,654
East Lindsey CCG	£63,328
Lincolnshire South West CCG	£61,444
Lincolnshire West CCG	£134,337
Skegness CCG	£84,440
South Holland CCG	£72,785
Welland CCG	£24,611
Lincolnshire	£484,601

Following atorvastatin patent expiry, rosuvastatin to atorvastatin switches are likely to release an additional annual saving in Lincolnshire of £1.45Mpa (assuming that the price of generic atorvastatin will fall to a level comparable with generic simvastatin and that 80% of rosuvastatin scripts are appropriate to switch to generic atorvastatin). The potential annual savings at CCG level from pursuing such a strategy are detailed below:

	Potential Annual Saving
Boston CCG	£134,400
East Lindsey CCG	£189,500
Lincolnshire SW CCG	£178,200
Lincolnshire West CCG	£398,000
Skegness CCG	£251,000
South Holland CCG	£215,000
Welland CCG	£81,000
Lincolnshire	£1.45M

PACEF Conclusions

The atorvastatin (Lipitor) patent expiry alone will potentially save £3.88Mpa across Lincolnshire. However, the full impact of this patent expiry is unlikely to be felt until 2013/14. Lincolnshire has high residual use of rosuvastatin and must tackle this problem to avoid continued investment in a high-cost long patent life statin until 2018. Rosuvastatin to atorvastatin switches are encouraged in 2012/13 in order to maximise the financial impact of the atorvastatin patent expiry as far as possible. Additional savings of £1.45Mpa across Lincolnshire could be achieved if rosuvastatin to atorvastatin switch programmes are implemented. The Prescribing and Medicines Management Team are developing resources for use in 2012/13 to support the implementation of this switch.

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

Dabigatran (Pradaxa): risk of serious haemorrhage – need for renal function testing

- A number of cases of serious and fatal haemorrhage have been reported in elderly patients with renal impairment who were receiving dabigatran.
- Renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with suspected decline in renal function,
- Dabigatran has a rapid onset of action and does not require therapeutic monitoring. It is eliminated unchanged in urine. Exposure to dabigatran is substantially increased in patients with renal insufficiency.
- To minimise the risk of bleeding, dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30mL/min).
- In moderate renal impairment (creatinine clearance 30 - 50mL/min), a dose reduction and close clinical surveillance should be considered, particularly in those at increased risk of bleeding. Similar precautions are advocated in those over 75.
- There is no specific antidote to dabigatran.
- There are a number of case reports of fatal haemorrhage with dabigatran for the prevention of systemic embolism in patients over 75 who had renal impairment and additional risk factors for bleeding (including concomitant medication). Half of the cases had severe renal impairment (a contra-indication for dabigatran).

- It is important to remember that haemorrhage is a well recognised adverse outcome of any anticoagulant; all patients at increased risk of bleeding require close monitoring.
- For warfarin, a dose reduction in elderly people should be considered and increased frequency of INR monitoring in patients at high risk of bleeding, including those with renal insufficiency.
- For rivaroxaban (Xarelto), caution is required in patients with severe renal impairment (creatinine clearance < 30mL/min) or moderate hepatic impairment. It is not recommended in patients with a creatinine clearance of less than 15mL/min.

Advice for healthcare professionals:

- Do not start dabigatran in any patient with severe renal impairment (creatinine clearance < 30mL/min).
- Assess renal function: (1) in all patients before starting dabigatran; (2) when a decline in renal function is suspected during treatment (e.g. hypovolaemia, dehydration or with some co-medications); (3) at least annually in patients over 75; (4) at least annually in patients with renal impairment.
- Check for signs of bleeding or anaemia and stop treatment if severe bleeding occurs.

PACEF Comment:
There is still no approved role for the use of dabigatran in Lincolnshire primary care. NICE have approved dabigatran for the prevention of venous thromboembolism after hip or knee replacement surgery in adults, although ULH prefer to use rivaroxaban for this indication (also approved by NICE). Both drugs are designated RED, with ULH providing the patient with the complete course. As discussed in *PACE Bulletin* Vol 5 No 17 (October 2011), dabigatran for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation remains RED-RED pending publication of the relevant NICE Technology Appraisal.

Angiotensin II receptor antagonists: evidence does not suggest any link with cancer

- The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has reviewed a possible link between ARBs and the occurrence of new cancers and has concluded that the evidence does not support any increased risk.

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