NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 5; Number 17 **October 2011**

What's new this month?

- **Dabigatran etexilate (Pradaxa) is evaluated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and is designated RED-RED (see page 3).**
- **NICE Clinical Guideline 126: *Management of stable angina* is detailed (see page 4).**
- **In response to NICE CG 126, ivabradine (Procoralan) and ranolazine (Ranexa) have been re-assessed and are now designated AMBER (see pages 7 and 8).**

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This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: SEPTEMBER 2011 UPDATE

Drug	Indication(s)	Traffic Light Status
Abatacept (Orencia) intravenous infusion	Licensed for moderate to severe active rheumatoid arthritis in combination with methotrexate in patients unresponsive to other disease modifying anti-rheumatic drugs	RED-RED
Bortezomib injection (Velcade)	Licensed for use in combination with melphalan and prednisolone for the treatment of previously untreated multiple myeloma in patients not	RED

	eligible for high dose chemotherapy with bone marrow transplantation	
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.
Dexamethasone intravitreal implant (Ozurdex)	Licensed for the treatment of adults with macular oedema following either branch retinal vein occlusion or central retinal vein occlusion.	RED
Golimumab injection (Simponi)	Licensed for the treatment of severe active ankylosing spondylitis when there is inadequate response to conventional treatment	RED
Ivabradine tablets (Procoralan)	Licensed for the treatment of angina in patients in normal sinus rhythm in combination with a beta-blocker or when BBs are contra-indicated or not tolerated	AMBER Ivabradine should only be initiated on the advice of a cardiologist
Nicorandil tablets (Ikorel)	Licensed for the prevention and long-term treatment of angina	GREEN Local cardiologists recommend nicorandil for patients who are nitrate intolerant in whom symptoms persist.
Ranolazine tablets (Ranexa)	Licensed as adjunctive therapy in the treatment of stable angina in patients inadequately controlled or intolerant of first-line anti-anginal therapies.	AMBER Ranolazine should only be initiated on the advice of a cardiologist
Thalidomide capsules (Thalidomide Celgene)	Licensed for use in combination with melphalan and prednisolone as first line treatment for untreated multiple myeloma in patients aged 65 and over or for those not eligible for high-dose chemotherapy	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 INDICATION ASSESSMENT: *DABIGATRAN FOR THE PREVENTION OF STROKE IN PATIENTS WITH ATRIAL FIBRILLATION*

Dabigatran etexilate (Pradaxa) is a direct thrombin inhibitor originally licensed for prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery. NICE evaluated dabigatran for this indication in September 2008 and approved it for use within the NHS. As a result of this PACEF designated dabigatran as RED for this indication (see *PACE Bulletin* Vol 2 No 18 (November 2008)).

Most recently, dabigatran has been granted an additional license 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).

The East Midlands Specialised Commissioning Group (EMSCG) has undertaken a preliminary assessment of dabigatran for this indication. The only Phase III trial available is the Randomised Evaluation of Long-term Anticoagulant Therapy (RE-LY) study. RE-LY is a drug-company funded, multicenter, prospective randomised drug trial with 18,113 participants recruited from 967 centres in 44 countries. Elements of the trial were blinded (e.g. dose of dabigatran (either 110mg or 150mg)) and the evaluation of all outcomes. It was a non-inferiority trial (i.e. it sought to show dabigatran to be as effective as warfarin). The average age of participants was 71 years, 64.3% of which were male and 50% were naïve to anticoagulants. Eligibility criteria for inclusion in the study meant by definition that all patients had a CHADS2 score ≥1 although 68% had a CHADS2 score of ≥ 2. The mean CHADS2 score was 2.1. Neither pulmonary embolism, hospitalisation nor all-cause mortality were significantly reduced in the dabigatran group compared with warfarin.

EMSCG conclude that current evidence ***does not*** suggest that dabigatran is superior to warfarin for the majority of patients with AF; nor is it cost-effective to substitute dabigatran for warfarin as warfarin remains effective, cost-effective and affordable. Concerns over the lack of evidence of long-term safety and efficacy of dabigatran in AF were also raised.

At a dose of 150mg twice daily, dabigatran will cost £2.52 per day or £920 per year. Taking into account the two recommended GP visits at £35 each, annual costs for dabigatran will be £990. This compares to a cost of approximately £500 per year for warfarin, including monitoring costs. As a result of this, dabigatran cannot be seen as a viable replacement therapy for warfarin at this time.

In addition to this, NICE are in the final stages of preparing their Technology Assessment of dabigatran for this indication due for publication in December 2011. The Appraisal Consultation Document published earlier in the summer stated that the Committee were not minded to recommend the use of dabigatran etexilate for the prevention of stroke or systematic embolism in people with AF. Further information, particularly in relation to cost-effectiveness, has been requested from the manufacturer.

PACEF Recommendation:
PACEF has significant concerns over the long-term efficacy, safety and cost-effectiveness of dabigatran for the prevention of stroke or systematic embolism in people with AF. As a result of this, dabigatran etexilate (Pradaxa) is designated RED-RED for this indication and should not be prescribed within this context in either secondary or primary care in Lincolnshire. This decision will be subject to review once NICE publish their TA within the next few months.

NICE CLINICAL GUIDELINE 126: *MANAGEMENT OF STABLE ANGINA* (JULY 2011)

Key Recommendations

- Optimal drug treatment of stable angina consists of one or two antianginal drugs as necessary plus drugs for secondary prevention of cardiovascular disease (CVD).

Drug Treatment

1. Nitrates
   Offer a short acting nitrate for preventing and treating angina and advise on correct administration and possible side effects.

2. Antianginal Drugs
   Offer either a beta blocker or calcium channel blocker (CCB) as first line treatment, based on co-morbidities, contraindications and patient preference. Do not routinely offer other antianginal drugs first line.

PACEF Comment:
Local cardiologists advise either a beta blocker first line or a CCB if intolerant; patients should be titrated up to the maximum tolerated dose.

If symptoms are not controlled on a beta blocker or CCB, switch to the other option or consider both drugs together. If combining a beta blocker with a CCB, use a dihydropyridine CCB (e.g. amlodipine, felodipine or slow release nifedipine).

PACEF Comment: Once Daily Dihydropyridine CCBs
Generic amlodipine tablets 5mg and 10mg are advocated as the dihydropyridine CCB of choice. The cost difference between different products is illustrated in the table below.

Calcium channel blockers	Dose	Cost for 28 days
Amlodipine tablets	**5mg daily** **10mg daily**	**£0.97** **£1.07**
Felodipine modified release tablets	2.5mg daily 5mg daily 10mg daily	£6.31 £4.21 £5.66
Nifedipine Adalat LA	30mg-90mg daily	£6.85-£15.88
Adalat Retard	10mg-40mg twice daily	£7.34-£17.62
Adipine MR	10mg-40mg twice daily	£3.73-£10.42
Adipine XL	30mg-90mg daily	£4.70-£11.80
Coracten SR	10mg-40mg twice daily	£3.64-£10.10
Coracten XL	30mg-90mg daily	£4.89-£12.23
Fortipine LA	40mg-80mg daily	£8.96-£17.92
Tensipine MR	10mg-40mg twice daily	£4.30-£10.98

Diltiazem - generic - Tildiem	60mg three times daily	£2.93 £7.43

Other antianginals may be considered if beta blockers and/or CCBs are contraindicated or not tolerated, e.g. long acting nitrate **or**
ivabradine **or**
nicorandil **or**
ranolazine

Choice should be based on co-morbidities, contraindications, patient preference and drug costs. If combining ivabradine with a CCB, use a dihydropyridine CCB (e.g. amlodipine, felodipine or slow release nifedipine).

PACEF Comment: Modified Release Mononitrates
If heart rate is controlled (≤70 BPM), consider adding a long acting nitrate. Where a once daily modified release isosorbide mononitrate (ISMN) preparation is indicated, prescribers are advised to standardise around a lower cost branded agent prescribed by brand name (e.g. Monomil XL). The cost difference between generically prescribed once daily ISMN formulations and both lower and higher cost brands is illustrated below.

Modified Release ISMN	**Dose**	**Cost for 28 days**
ISMN MR 25mg tablets (Tariff)	25mg daily	£5.95
ISMN MR 25mg capsules (Tariff)	25mg daily	£6.30
ISMN MR 25mg capsules (Elantan LA)	25mg daily	£2.64
ISMN MR 25mg capsules (Isodur 25XL)	25mg daily	£5.50
ISMN MR 25mg tablets (Isotard 25XL)	25mg daily	£5.95
ISMN MR 40mg tablets (Ismo Retard)	40mg daily	£9.10
ISMN MR 40mg tablets (Isotard 40XL)	40mg daily	£6.75
ISMN MR 40mg capsules (Monomax SR)	40mg daily	£6.52
ISMN MR 40mg tablets (Zemon 40 XL)	40mg daily	£14.25
ISMN MR 50mg tablets (Tariff)	50mg daily	£6.75
ISMN MR 50mg capsules (Tariff)	50mg daily	£15.07
ISMN MR 50mg capsules (Elantan LA)	50mg daily	£3.69
ISMN MR 50mg capsules (Isodur 50XL)	50mg daily	£6.50
ISMN MR 50mg tablets (Isotard 50XL)	50mg daily	£6.75
ISMN MR 60mg tablets (Tariff)	60mg daily	£10.50
ISMN MR 60mg capsules (Tariff)	60mg daily	£8.66
ISMN MR 60mg tablets (Monomil® XL)	**60mg daily**	**£3.49**
ISMN MR tablets 60mg (Chemydur 60XL)	60mg daily	£3.99
ISMN MR tablets 60mg (Imdur)	60mg daily	£10.50
ISMN MR tablets 60mg (Isib 60XL)	60mg daily	£8.15
ISMN MR 60mg tablets (Isotard 60XL)	60mg daily	£5.75
ISMN MR 60mg tablets (Modisal XL)	60mg daily	£10.36
ISMN MR 60mg tablets (Monomax XL)	60mg daily	£5.25
ISMN MR 60mg capsules (Monomax XL)	60mg daily	£8.86
ISMN MR 60mg tablets (Monosorb XL 60)	60mg daily	£16.66
ISMN MR 60mg tablets (Zemon 60	60mg daily	£11.14

XL)		
ISMN MR 60mg tablets (Xismox XL)	60mg daily	£5.51

PACEF Comment: Nicorandil (Ikorel)
Local cardiologists recommend nicorandil for patients who are nitrate intolerant in whom symptoms persist. Within this context nicorandil (Ikorel) is designated: GREEN.

A third antianginal drug should only be offered when:

- two antianginal drugs do not satisfactorily control symptoms **and**
- the person is waiting for revascularisation or revascularisation is not appropriate or acceptable.

PACEF Comment: Other Third Line Antianginal Drugs
The cost comparison below illustrates the relative costs of modified release ISMN, nicorandil (Ikorel), ivabradine (Procoralan) and ranolazine (Ranexa). PACEF have not historically supported the use of either ivabradine (Procoralan) or ranolazine (Ranexa), but have undertaken a re-assessment of both drugs in response to this Clinical Guideline. The results of the ivabradine re-assessment are published below. Ranolazine (Ranexa) is due for review at the October PACEF meeting.

Other antianginals	Dose	Cost for 28 days
ISMN MR 60mg tablets (Tariff)	60mg daily	£10.50
ISMN MR 60mg tablets (Monomil® XL)	60mg daily	£3.49
Nicorandil tablets (Ikorel)	10mg twice daily	£7.20
	20mg twice daily	£13.66
Ivabradine tablets (Procoralan)	5mg twice daily	£40.17
	7.5mg twice daily	£40.17
Ranolazine tablets (Ranexa)	375mg twice daily	£45.71
	500mg twice daily	£45.71
	750mg twice daily	£45.71

3. Secondary Prevention
   - Offer a statin in line with NICE CG 67.

PACEF Comment:
Simvastatin 40mg should be prescribed first line in accordance with local lipid management guidelines. If not tolerated, consider pravastatin 40mg. Where a higher cost higher potency statin becomes necessary due to poor tolerability or insufficient response, atorvastatin should be preferred.

- Offer treatment for high blood pressure in line with NICE CG 127.

PACEF Comment:
NICE Clinical Guideline 127: *Hypertension* (August 2011) will be reviewed at PACEF next month and will be featured in a forthcoming edition of the *PACE Bulletin.*

- Consider aspirin 75mg taking into account the risk of bleeding and co-morbidities.

PACEF Comment:
If the patient is intolerant to aspirin 75mg, consider a low cost concurrent PPI. If the patient has a genuine allergy to aspirin, consider generic clopidogrel as an alternative.

- Consider angiotensin converting enzyme inhibitors (ACEI) in people with stable angina and diabetes. Offer or continue ACEI for other conditions in line with relevant NICE guidance.
- Do not offer prescriptions for vitamins or fish oil supplements.

PACEF Comment
Prescribers are reminded that Omacor capsules (omega-3 acid ethyl esters) are not recommended for use. Designation: RED-RED.

- If symptoms are not satisfactorily controlled with optimal drug treatment, consider revascularisation (coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]).
- CABG is also an option for those whose symptoms are satisfactorily controlled on optimal drug treatment to improve prognosis in a sub group of people with left main stem or proximal three vessel disease.

REVIEW: *IVABRADINE 5MG AND 7.5MG TABLETS (PROCORALAN)*

Ivabradine (Procoralan) is a heart rate-lowering agent, lowering heart rate both at rest and during exercise. It is licensed for the treatment of chronic stable angina in patients in normal sinus rhythm in combination with a beta blocker or when beta blockers are contraindicated or not tolerated.

NICE reviewed trials comparing ivabradine monotherapy to placebo, atenolol and amlodipine. They found that short term trials of ivabradine versus atenolol or amlodipine showed similar increases in total exercise duration and similar reductions in the frequency of angina episodes in both treatment groups. The addition of ivabradine to atenolol monotherapy resulted in small increases in total exercise duration and time to angina on the treadmill, but did not reduce the frequency of angina episodes. From this NICE concluded that there was sufficient trial evidence to show that ivabradine is an effective antianginal agent with comparable short term efficacy to atenolol and amlodipine. No trial evidence supporting the use of ivabradine in combination with a CCB was identified.

NICE identified significantly higher rates of adverse events in ivabradine treated patients in trials, partly due to visual disturbances (e.g. blurred vision). Other documented side effects include bradycardia and heart block. They also emphasized that evidence of long-term safety and efficacy is lacking. The cost comparison above illustrates that ivabradine is significantly higher in cost than most other antianginal treatments (except ranolazine).

PACEF Recommendation:
PACEF have reviewed the ULH Drug and Therapeutics Committee and NICE assessment of ivabradine (Procoralan) and have re-classified ivabradine as AMBER without shared care. Ivabradine should only be initiated on the advice of a cardiologist and should only be used within licensed indications (i.e. for the treatment of chronic stable angina in patients in normal sinus rhythm in combination with a beta blocker or when beta blockers are contraindicated or not tolerated). Local cardiologists recommend that ivabradine should be

considered in patients with a heart rate ≥70 beats per minute where combination BB and CCB therapy is compromised due to intolerance of one of the components or insufficient effectiveness of BB/CCB combination therapy. NICE have emphasized that a third antianginal drug can only added in to therapy where two antianginal drugs do not satisfactorily control symptoms and the person is waiting for revascularisation or revascularisation is not appropriate or acceptable.

REVIEW: *RANOLAZINE 375MG, 500MG AND 750MG TABLETS (RANEXA)*

Ranolazine (Ranexa) is licensed as adjunctive therapy in the treatment of stable angina in patients inadequately controlled or intolerant of first-line anti-anginal therapies. PACEF originally reviewed ranolazine in May 2010 and were concerned over the short duration of the trials, the modest benefits demonstrated and the variance between the licensed dose of the drug and the doses used in trials. In addition, the drug interactions with commonly used concurrent therapies, the narrow therapeutic index and the relatively poor cost effectiveness also gave cause for concern. As a result of this, ranolazine was originally designated RED-RED and not approved for use in either primary or secondary care (see *PACE Bulletin*, Vol 4 No 9 (June 2010).

The recently published NICE clinical guideline for stable angina (as detailed above) recommends ranolazine as one of the treatment options for patients who cannot tolerate BBs and CCBs or for whom they are contraindicated; other options are long-acting nitrates, nicorandil and ivabradine. Ranolazine is also recommended as one of the additional treatments to consider in patients taking a BB or CCB whose symptoms are not controlled and the other option (BB or CCB) is not tolerated or contraindicated. Endorsement of ranolazine monotherapy by NICE takes the drug outside of licensed indications as ranolazine is only licensed for use in combination therapy.

Evidence to support the long term use of ranolazine as adjunctive anti-anginal therapy is very limited, with clinical improvements in terms of increased exercise time and reduction in symptom severity classed as modest and judged to be of uncertain clinical significance. Trials also included the unlicensed higher dose of ranolazine of 1000mg twice daily. Evidence of long term efficacy and safety is still lacking. Nonetheless, the NICE guideline development group concluded that, although there is insufficient evidence to recommend the routine use of ranolazine, it may have a role in people with stable angina who are inadequately controlled or intolerant of first-line therapies.

The cost of ranolazine is substantially higher than the cost of other first-line antianginal drugs, such as long acting nitrates and nicorandil, and slightly higher than ivabradine (see above). Ranolazine also has a narrow therapeutic margin with respect to safety and tolerability and has been implicated in a wide range of drug interactions which will limit its use as many patients with stable angina are also receiving other medication to treat co-existing medical conditions.

PACEF Recommendation:
PACEF have reviewed the NICE assessment of ranolazine (Ranexa) and have re-classified ranolazine as AMBER without shared care. Ranolazine should only be initiated on the advice of a cardiologist and should only be used within licensed indications (i.e. as adjunctive therapy in the treatment of stable angina in patients inadequately controlled or intolerant of first-line anti-anginal

therapies). Local cardiologists recommend that ranolazine should only be considered in those patients intolerant to BBs/ CCBs who have a controlled heart rate but still have persistent symptoms despite receiving the maximum tolerated dose of a long acting nitrate or nicorandil. Local guidance does not recognise any role for ranolazine monotherapy. NICE have emphasized that a third anti-anginal drug can only added in to therapy where two anti-anginal drugs do not satisfactorily control symptoms and the person is waiting for revascularisation or revascularisation is not appropriate or acceptable.

NICE TECHNOLOGY APPRAISAL 228: *BORTEZOMIB AND THALIDOMIDE FOR THE FIRST-LINE TREATMENT OF MULTIPLE MYELOMA* (JULY 2011)

Key Recommendations

Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the **first-line treatment of multiple myeloma** in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.

Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the **first-line treatment of multiple myeloma** if:

- high-dose chemotherapy with stem cell transplantation is considered inappropriate *and*
- the person is unable to tolerate or has contraindications to thalidomide.

PACEF Recommendation:
Bortezomib injection (Velcade) and thalidomide capsules (Thalidomide Celgene) are designated RED for the first-line treatment of multiple myeloma.

NICE TECHNOLOGY APPRAISAL 229: *DEXAMETHASONE INTRAVITREAL IMPLANT FOR THE TREATMENT OF MACULAR OEDEMA SECONDARY TO RETINAL VEIN OCCLUSION* (JULY 2011)

Key Recommendations

Dexamethasone intravitreal implant is recommended as an option for the **treatment of macular oedema following central retinal vein occlusion**.

Dexamethasone intravitreal implant is recommended as an option for the **treatment of macular oedema following branch retinal vein occlusion** when:

- treatment with laser photocoagulation has not been beneficial, **or**
- treatment with laser photocoagulation is not considered suitable because of the extent of macular haemorrhage.

PACEF Recommendation:
Dexamethasone intravitreal implant (Ozurdex) is designated RED for the treatment of adults with macular oedema following either branch retinal vein occlusion or central retinal vein occlusion.

NICE TECHNOLOGY APPRAISAL 233: *GOLIMUMAB FOR THE TREATMENT OF ANKYLOSING SPONDYLITIS* (AUGUST 2011)

Key Recommendations

Golimumab is recommended as an option for the treatment of severe, active ankylosing spondylitis in adults only if:

- it is used as described for adalimumab and etanercept in 'Adalimumab, etanercept and infliximab for ankylosing spondylitis' (see NICE TA 143) **and**
- the manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose in accordance with the patient access scheme.

PACEF Recommendation:
Golimumab injection (Simponi) is designated RED for the treatment of severe, active ankylosing spondylitis.

NICE TECHNOLOGY APPRAISAL 234: *ABATACEPT FOR THE TREATMENT OF RHEUMATOID ARTHRITIS AFTER THE FAILURE OF CONVENTIONAL DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS* (AUGUST 2011)

Key Recommendations

Abatacept in combination with methotrexate is not recommended for the treatment of moderate to severe active rheumatoid arthritis in adults whose disease has responded inadequately to one or more conventional non biological disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate.

PACEF Recommendation:
Abatacept (Orencia) intravenous infusion is designated RED-RED for the treatment of moderate to severe RA.

SHARED CARE GUIDELINES

Following the September PACEF meeting the following shared care guideline has been approved for use:

- *Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease*, 4th Edition (June 2011)

All of the associated drugs are designated as AMBER (see *PACE Bulletin* Vol 5 No 11 (June 2011)). Copies of the shared care guideline should be provided by specialist services in conjunction with any request for GPs to prescribe. Copies of the SCG are available on the NHS Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATES (AUGUST AND SEPTEMBER 2011)*

Withdrawal of Onsenal (Celecoxib)

Celecoxib is a non-steroidal anti-inflammatory drug and cyclo-oxygenase type 2 inhibitor (Cox-2 inhibitor) licensed for the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. It is also licensed as the orphan drug Onsenal for

the reduction of intestinal polyps in familial adenomatous polyposis (FAP). **The EMA has withdrawn the marketing authorisation for Onsenal because of concerns about the increased cardiovascular and gastrointestinal side effects of celecoxib used at high dose and long-term in patients with FAP.**

Systemic fusidic acid and interaction with statins: risk of rhabdomyolysis

The increased risk of rhabdomyolysis when systemic fusidic acid is used concomitantly with statins was highlighted by the MHRA in January 2008. In recent years the number and severity of reports of rhabodomyolysis (including a report of a fatality) have increased. Whilst numbers of reported cases are still low, the increasing number of reports indicate that some clinicians may not be aware of this potentially serious interaction.

The MHRA have issued the following advice to healthcare professionals:

- **Systemic fusidic acid should not be given with statins because of the risk of potentially fatal rhabdomyolysis.**
- In patients treated with a statin where systemic fusidic acid is considered essential, statin therapy should be temporary discontinued throughout the duration of fusidic acid treatment and not restarted until 7 days after the last dose of systemic fusidic acid.
- In exceptional cases where prolonged systemic fusidic acid treatment is necessary, the need for co-administration of a statin should be considered on an individual basis and only under close medical supervision.
- Patients should be advised to seek immediate medical advice if they experience any symptoms of muscle weakness, pain, or tenderness.
- Any muscle symptoms reported in patients prescribed statins should be followed up.

Antipsychotics use during third trimester of pregnancy

A recent Europe wide review has concluded that there is a risk of extrapyramidal effects or withdrawal symptoms (or both) in newborns after maternal use of antipsychotics during the third trimester of pregnancy. There is insufficient data to determine the size or any differences in risk between individual or different classes of antipsychotics.

The MHRA have issued the following advice to healthcare professionals:

- Following maternal use of antipsychotics in the third trimester, examine newborns for symptoms which may include agitation, hypertonia, hypotonia, tremor, somnolence, feeding problems and respiratory distress.
- Symptoms may vary in severity and duration and should be monitored and treated on an individual basis.
- Expectant mothers should be counselled about the benefits and risks of antipsychotic treatment during pregnancy.

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