NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 4; Number 9 **June 2010**

What's new this month:

- **Doxycycline 40mg modified release (Efracea) has not been approved for the treatment of facial rosacea. Designation: RED-RED (see page 3).**
- **Febuxostat tablets (Adenuric) are approved for the management of chronic hyperuricaemia in gout for people who are intolerant of allopurinol or for whom allopurinol is contraindicated. Designation: GREEN (see page 4).**
- **Lacosamide (Vimpat) has been approved for the adjunctive treatment of partial seizures. It can be prescribed in primary care following specialist initiation. Designation: AMBER (see page 5).**
- **Ranolazine modified release (Ranexa) has not been approved for the treatment of stable angina. Designation: RED-RED (see page 6).**
- **Prasugrel 5mg (Efient) has been approved for GP prescribing within licensed indications for patients with *clopidogrel hypersensitivity or following stent insertion in those who have been shown to be clopidogrel resistant (suggested in those presenting with stent thrombosis or recurrent events on combination aspirin and clopidogrel).* Treatment must be initiated by a cardiologist and is not subject to a shared care guideline. Designation: AMBER. For all other indications prasugrel remains RED subject to review (see page 7).**
- **Two incidents related to prescribing/dispensing errors with oral tacrolimus have recently occurred in Lincolnshire; this is symptomatic of a wider problem across the country identified by the MHRA. Prescribers should ensure that all prescribing of tacrolimus preparations is by brand name to avoid confusion (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.lpct.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

SUMMARY OF PACEF DECISIONS: MAY 2010 UPDATE

Drug	Indication(s)	Traffic Light Status
Doxycycline 40mg modified release capsules (Efracea)	Licensed to reduce papulopustular lesions in adult patients with facial rosacea without ocular involvement.	RED-RED
Febuxostat 80mg and 120mg tablets (Adenuric)	Licensed for chronic hyperuricaemia where deposition has occurred.	GREEN N.B Should only be used second line after allopurinol in people who are intolerant of allopurinol or for whom allopurinol is contraindicated.
Lacosamide tablets and syrup 15mg per ml (Vimpat)	Licensed for use as an adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.	AMBER N.B. No shared care guideline is required; should only be prescribed in primary care following specialist initiation.
Lacosamide intravenous infusion 200mg vial (Vimpat)	Licensed for use as an adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients with epilepsy aged 16 years and older.	RED
Prasugrel tablets 5mg (Efient)	Licensed for use in combination with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing percutaneous coronary intervention	RED N.B. PACEF have approved an AMBER classification allowing GP prescribing within licensed indications for patients with *clopidogrel hypersensitivity or following stent insertion in those who have been shown to be clopidogrel resistant.* Treatment must be initiated by a cardiologist and is not subject to a shared care guideline.
Ranolazine MR tablets (Ranexa)	Licensed as an adjunctive therapy in the treatment of stable angina in patients inadequately controlled or intolerant of first-line antianginal therapies	RED-RED
Sulphamethoxypyridazine 500mg tablets	Unlicensed. Used for IgA related bullous diseases in patients intolerant of dapsone.	RED Should not be prescribed in primary care.

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 within licensed indications**. 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.**

RAPID DRUG ASSESSMENT: DOXYCYCLINE 40MG MODIFIED RELEASE CAPSULES (EFRACEA)

Doxycycline 40mg modified release (MR) (Efracea) is the first doxycycline formulation licensed for the treatment of facial rosacea. Whilst doxycycline has been a recognised treatment for this condition for some time, none of the previously existing preparations are licensed for this purpose. Conventionally, doxycycline 100mg daily, a systemic antibacterial dose, has been prescribed for moderately severe acne. Doxycycline 40mg MR capsules (Efracea) contain a sub-antimicrobial dose of doxycycline which, nonetheless, appears to have anti-inflammatory properties. The manufacturers claim that this dose should carry a lower risk of intestinal bacterial resistance, although this has yet to be demonstrated in clinical trials.

Clinical evidence from two 16 week placebo controlled randomized controlled trials demonstrate a reduction in the number of lesions with active treatment and no effect on other symptoms such as the incidence of nodules and the extent and severity of erythema. There are no comparative trials against any other alternative treatment.

Acne is a chronic inflammatory condition involving the hair follicle and associated sebaceous gland. Management of the condition is dependent upon severity and whether the condition is mainly inflammatory (where pustules and papules predominate) or comedonal (where blackheads and whiteheads predominate).

The United Lincolnshire Hospitals Trust *Dermatology Handbook* (4th edition 2008) recommends a stepwise approach to the treatment of acne as follows:

Mild

Comedonal: Use keratolytics (e.g. topical retinoid) or topical azelaic acid
Inflammatory: Use benzyl peroxide initially 2.5% or topical antibiotics (e.g. clindamycin or erythromycin)

Moderate

Oral antibiotics (e.g. oxytetracycline 500mg twice daily, lymecycline 408mg daily, minocycline 100mg daily, doxycycline100mg daily, erythromycin 500mg twice daily or clarithromycin 500mg twice daily

Severe

Add oral contraceptive (female patients only) or isotretinoin.

A cost comparison of doxycycline 40mg modified release (Efracea) with other alternative treatments reveals the following:

Drug	Daily dose range	Cost (£) 4 months
Efracea Doxycycline m.r	40mg once daily	£59.56
Oral antibiotics		
doxycycline	100mg daily	£7.79
lymecycline	408mg daily	£31.08
oxytetracycline	500mg twice daily	£21.44
Topical antibiotics		
Clindamycin aq lotion(Dalacin T)*	Apply twice daily	£33.88
Erythromycin (Zineryt)**	Apply twice daily	£66.72
Metronidazole (Acea)***	Apply twice daily	£19.90
Metronidazole (Rosiced)+	Apply twice daily	£15.00

* based on 4 x 50ml being used
** based on 4 x 90ml being used.
*** 8 weeks treatment using 2x40g
+ 6 weeks treatment using 2 x 30g

PACEF Recommendation:
Trial evidence supporting the use of doxycycline 40mg modified release is limited to two placebo controlled RCTs and no comparative trials against established alternatives; claims that this lower dose of doxycycline results in a lower incidence of intestinal bacterial resistance have yet to be substantiated. In addition, a cost comparison reveals that Efracea is significantly more expensive than most of the alternative preparations advocated in local acne treatment guidance. As a result of this, doxycycline 40mg modified release capsules (Efracea) are designated RED-RED.

RAPID DRUG ASSESSMENT: FEBUXOSTAT TABLETS (ADENURIC)

Over a year after the publication of NICE Technology Appraisal 164: *Febuxostat for the management of hyperuricaemia in people with gout* (December 2008), Menarini have launched febuxostat tablets 80mg and 120mg in the UK. NICE recommendations in December 2008 were as follows:

- Febuxostat (Adenuric), within its marketing authorisation, is recommended as an option for the management of chronic hyperuricaemia in gout **only** for people who are intolerant of allopurinol or for whom allopurinol is contraindicated.
- Intolerance to allopurinol is defined as adverse effects that are sufficiently severe as to warrant either discontinuation or conservative dosing that prevents full dose escalation and the achievement of optimal effectiveness.

Febuxostat (Adenuric) is a non-purine selective inhibitor of xanthine oxidase that achieves its therapeutic effect by decreasing uric acid concentration.
It is licensed for the treatment of chronic hyperuricaemia in conditions where urate/uric acid deposition has already occurred (including a history or the presence of tophi and/or gouty arthritis).

NICE reviewed five studies as part of their appraisal. Febuxostat appears from trial evidence to be more effective at reducing serum uric acid concentration than fixed–dose allopurinol. However, fully titrated allopurinol is recommended as best practice and there is no trial evidence comparing febuxostat with a fully titrated dose schedule of allopurinol. Further evidence is required to demonstrate whether febuxostat has any advantage over allopurinol in terms of gout flare control, reduction in tophi size and number and avoidance of longer term joint and organ damage.

As part of their appraisal, NICE expressed concern over the increased proportion of recurrent gout flares with febuxostat. Specialist advice has reassured them that this is likely to be linked to rate of change of serum uric acid concentration, with treatments that reduce serum uric acid concentration most effectively and rapidly having a most pronounced effect. NICE remain concerned over the higher number of cardiovascular events and deaths across the febuxostat arms of the APEX, FACT and EXCEL studies. In order to minimize this risk, the marketing authorisation for rebuxostat precludes use in patients with ischaemic heart disease and congestive heart failure.

A cost comparison of febuxostat against allopurinol reveals that the new product is significantly more expensive:

	Dose	28 day cost
Allopurinol 100mg tablets (generic)	100mg daily	£1.19
Allopurinol 300mg tablets (generic)	300mg daily	£1.32
Febuxostat 80mg tablets (Adenuric)	80mg once daily	£24.36
Febuxostat 120mg tablets (Adenuric)	120mg once daily	£24.36

NICE have also undertaken a cost-effectiveness analysis and retain concerns over the cost-effectiveness of febuxostat in comparison to allopurinol. As a result of this, febuxostat can only be supported for NHS use as a second line therapy for the management of gout **only** in people who are intolerant of allopurinol or for whom allopurinol is contraindicated.

PACEF Recommendation
Febuxostat tablets (Adenuric) are designated GREEN. Febuxostat can be initiated in primary care for the treatment of chronic hyperuricaemia, but only as a second line agent in people intolerant of allopurinol or for whom allopurinol is contraindicated. Prescribers are reminded that the drug should not be used in patients with ischaemic heart disease and congestive heart failure.

NEW DRUG ASSESSMENT: LACOSAMIDE TABLETS, SYRUP AND INFUSION (VIMPAT)

Lacosamide (Vimpat) is a new antiepileptic drug (AED) licensed for use as an adjunctive treatment of partial onset seizures with or without secondary generalisation in adult patients with epilepsy. The efficacy and safety of oral lacosamide have been established in three RCTs involving adjunctive use in patients with uncontrolled partial onset seizures who are already taking up to three concomitant anti-epileptic drugs. The results from all three trials showed that oral lacosamide 400mg per day was associated with a statistically significant decrease in seizure frequency compared to placebo. There are no comparative trials between lacosamide and other anti-epileptic drugs. Data from a long term extension study following a phase II clinical trial showed a median 45.9% reduction in seizure frequency for continued use up to 36 months.

Dose related adverse effects include dizziness, headache, fatigue, ataxia, vertigo, nausea and vomiting. In clinical trials, lacosamide has not significantly affected plasma concentrations of carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate or valproic acid.

PACEF Recommendation:
PACEF approved lacosamide tablets and syrup (Vimpat) for consultant initiation only. Designation: AMBER. No shared care guideline is required, but GPs can prescribe subject to specialist initiation. ULHT Drug and Therapeutics Committee have also approved lacosamide infusion for use within secondary care only. Designation: RED.

NEW DRUG ASSESSMENT: RANOLAZINE MODIFIED RELEASE TABLETS (RANEXA)

Ranolazine MR (Ranexa) is an anti-anginal agent licensed as an add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies.

PACEF reviewed two clinical trials, both of relatively short duration. The first ran for 12 weeks and compared ranolazine 750mg twice daily, 1000mg twice daily and placebo as add-on therapies to current angina medication in 823 patients with chronic stable angina of at least 3 months' duration. Modest, but statistically significant, improvements were found in the ranolazine groups in exercise treadmill performance; a reduced frequency of angina attacks and use of glyceryl trinitrate was also linked to the active treatment. In the second study, 565 patients with chronic angina on the maximum dose of amlodipine were randomised to receive ranolazine 500mg twice daily for one week followed by 1000mg twice daily for 6 weeks or placebo. The primary endpoint was the mean weekly frequency of angina episodes and this was significantly lower in the ranolazine group. Both of these trials used doses of ranolazine above the currently recommended maximum dose of 750mg twice daily.

The most frequently reported adverse effects in clinical trials were constipation, dizziness and nausea. Some patients are at increased risk of adverse effects including: the elderly, those above 60kg bodyweight, those with mild renal or hepatic impairment or those with congestive heart failure. Ranolazine is contra-indicated in severe renal impairment and in moderate or severe hepatic impairment. It also interacts with a wide variety of medicines, including several which are likely to be co-prescribed (e.g. diltiazem, digoxin and simvastatin)
In primary care, ranolazine costs £48.98 per patient per month. It has not been recommended by the Scottish Medicines Consortium for use in NHS Scotland or by the All Wales Medicines Strategy Group for use in NHS Wales due to concerns over cost-effectiveness.

PACEF Recommendation:
PACEF were concerned about 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 the trials. The drug interactions with commonly used concurrent therapies, the narrow therapeutic index and relatively poor cost-effectiveness also gave cause for concern. As a result of this, ranolazine MR tablets (Ranexa) were designated RED-RED.

RAPID DRUG ASSESSMENT: SULPHAMETHOXYPYRIDAZINE 500MG TABLETS (UNLICENSED)

Sulphamethoxypyridazine is a long-acting sulphonamide used in Immunoglobulin A (IgA) related bullous diseases such as dermatitis herpetiformis, Linear IgA disease and IgA pemphigus. It is unlicensed in the UK, but can be imported as the branded formulation Lederkyn. It has recently been approved for specialist use only within ULHT as an alternative treatment for IgA related bullous diseases in patients who are intolerant of dapsone.

PACEF Recommendation:
Sulphamethoxypyridazine 500mg tablets are designated RED for IgA related bullous diseases in patients intolerant of dapsone. Under no circumstances should this product be prescribed in primary care.

RAPID REVIEW: PRASUGREL TABLETS 5MG (EFIENT)

Additional PACEF Recommendation:
Following a request from local cardiologists and in conjunction with ULHT Drug and Therapeutics Committee, PACEF have approved prasugrel (Efient) for GP prescribing within licensed indications for patients with clopidogrel hypersensitivity or following stent insertion in those who have been shown to be clopidogrel resistant (suggested in those presenting with stent thrombosis or recurrent events on combination aspirin and clopidogrel). For these indications, prasugrel is re-designated as AMBER; initiation should be by a cardiologist; following initiation prescribing can continue in primary care; no shared care guideline is required. Discussions over a broader role for prasugrel compliant with NICE TA 182 continue with local cardiologists and the East Midlands Cardiac Network. Until a final position is agreed, prasugrel remains RED for all other indications.

Prescribers are reminded of the key recommendations of NICE TA 182: *Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention* (October 2009):

> Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention only when:
> - immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary or
> - stent thrombosis has occurred during clopidogrel treatment or the patient has diabetes mellitus.

The TRITON-TIMI 38 study shows some advantages with prasugrel in terms of effectiveness, including statistically significant reductions in a composite endpoint, non-fatal MI and stent thrombosis compared to clopidogrel. In terms of safety, an increased rate of major bleeds (including fatal bleeds) occurred with prasugrel compared with clopidogrel. Overall, all-cause mortality, CV death and non-fatal stroke did not differ significantly between groups. NICE conclude that prasugrel and clopidogrel are broadly equivalent in terms of clinical effectiveness at 15 months for patients with ACS having PCI.

In terms of cost-effectiveness, NICE have concluded that prasugrel is only cost-effective in the sub-groups identified. Since they issued their guidance the generic price of clopidogrel has fallen significantly as illustrated in the cost comparison below:

Drug	Daily dose	28 day cost
Prasugrel 5mg tablets (Efient)	5mg daily	£47.56
Prasugrel 10mg tablets (Efient	10mg daily	£47.56
Clopidogrel 75mg tablets (Plavix)	75mg daily	£33.93
Clopidogrel 75mg tablets (generic)	75mg daily	£10.17

(Prices derived from Drug Tariff June 2010 and MIMS June 2010)

PACEF Comment:
Further discussions on an expanded role for prasugrel will focus on safety concerns, cost-effectiveness and role in the sub-groups identified by NICE. Until these discussions are completed, prasugrel is not recommended for GP prescribing apart from in the exceptional circumstances identified above.

SHARED CARE GUIDELINES

PACEF have approved the following shared care guidelines for use:

- Methotrexate in Rheumatology
- Sulfasalazine in Rheumatology
- Sirolimus for Maintenance of Immunosuppression after Kidney Transplantation in Adults
- Tacrolimus for the Maintenance of Immunosuppression after Kidney Transplantation in Adults

Approaches from specialists to GPs requesting participation in shared care should be accompanied by a copy of the relevant SCG. Any queries relating to shared care or interface related issues or requests for particular SCGs should be addressed to Cathy Johnson, Interface Lead Pharmacist at cathy.johnson@lpct.nhs.uk

NICE CLINICAL GUIDELINE 95: *CHEST PAIN OF RECENT ONSET* (MARCH 2010)

The key recommendations are as follows:

Presentation with acute chest pain

- Take a resting 12-lead electrocardiogram (ECG) as soon as possible. When people are referred, send the results to hospital before they arrive if possible. Recording and sending the ECG should not delay transfer to hospital.
- Do not exclude an acute coronary syndrome (ACS) when people have a normal resting 12-lead ECG.
- Do not routinely adminster oxygen, but monitor oxygen saturation using pulse oximetry as soon as possible, ideally before hospital admission. Only offer supplemental oxygen to:
    - people with oxygen saturation SpO_2 of less than 94% who are not at risk of hypercapnic respiratory failure, aiming for SpO_2 of 94-98%
    - people with chronic obstructive pulmonary disease who are at risk of hypercapnic respiratory failure, to achieve a target SpO_2 of 88-92% until blood gas analysis is available.

Do not assess symptoms of an ACS differently in ethnic groups. There are no major differences in symptoms of an ACS among different ethnic groups.

Presentation with stable chest pain

- Diagnose stable angina based on one of the following:
    - clinical assessment alone or
    - clinical assessment plus diagnostic testing (that is, anatomical testing for obstructive coronary artery disease (CAD) and/or functional testing for myocardial ischaemia).

- If people have features of typical angina based on clinical assessment and their estimated likelihood of CAD is greater than 90%, further diagnostic investigation is unnecessary. Manage as angina.
- Unless clinical suspicion is raised based on other aspects of the history and risk factors, exclude a diagnosis of stable angina if the pain is non-anginal. Other features which make a diagnosis of stable angina unlikely are when the chest pain is:
    - continuous or very prolonged and/or
    - unrelated to activity and/or
    - brought on by breathing in and/or
    - associated with symptoms such as dizziness, palpitations, tingling or difficulty swallowing.

  Consider causes of chest pain other than angina (such as gastrointestinal or musculoskeletal pain).
- In people without confirmed CAD, in whom stable angina cannot be diagnosed or excluded based on clinical assessment alone, estimate the likelihood of CAD. Take the clinical assessment and the resting 12-lead ECG into account when making the estimate. Arrange further diagnostic testing as follows:
    - if the estimated likelihood of CAD is 61-90%, offer invasive coronary angiography as the first-line diagnostic investigation if appropriate.
    - if the estimated likelihood of CAD is 30-60%, offer functional imaging as the first-line diagnostic investigation.
    - if the estimated likelihood of CAD is 10-29%, offer CT calcium scoring as the first-line diagnostic investigation.
- Do not use exercise ECG to diagnose or exclude stable angina for people without known CAD.

People presenting with acute chest pain
Check for a suspected ACS

- Check immediately if chest pain is current, or when the last episode was, particularly if in the last 12 hours.
- Check if the chest pain may be cardiac. Consider:
    - history of pain
    - any cardiovascular risk factors
    - history of ischaemic heart disease and any previous treatment
    - previous investigations for chest pain
- Check if any of the following symptoms of ischaemia are present. These may indicate an ACS:
    - Pain in the chest and/or other areas (for example, the arms, back or jaw) lasting longer than 15 minutes.
    - Chest pain with nausea and vomiting, marked sweating or breathlessness (or a combination of these), or with haemodynamic instability.
    - New onset chest pain, or abrupt deterioration in stable angina, with recurrent pain occurring frequently with little or no exertion and often lasting longer than 15 minutes.
- Central chest pain may not be the main symptom.
- Do not use response to glyceryl trinitrate (GTN) to make a diagnosis of ACS.
- Do not assess symptoms of an ACS differently in men and women or among different ethnic groups.
- Advise people about seeking medical help if they have further chest pain.

- If the chest pain is non-cardiac, explain this to the person and refer for further investigation if appropriate.
- If the chest pain is suspected to be an ACS follow the pathway in the NICE CG.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (MAY 2010)

SSRIs and SNRIs: risk of persistent pulmonary hypertension in the new born

- Epidemiological data suggest that **the use of selective serotonin reuptake inhibitors (SSRIs) in pregnancy, particularly in the later stages, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN).** The observed increase in risk is from the background rate in the general population of 1-2 cases per 1000 pregnancies to approximately 5 cases per 1000 pregnancies.
- A retrospective study reported an increased risk after 20 weeks gestation, but no increased risk before 20 weeks.
- There is no evidence of a similar association between serotonin and noradrenaline reuptake inhibitors (SNRIs) and PPHN, but the potential risk cannot be ruled out due to the related mechanisms of action.

Advice to healthcare professionals:

- Healthcare professionals are encouraged to enquire about the use of these medicines, particularly in women in the later stages of pregnancy.
- Close observation of neonates exposed to SSRIs or SNRIs for signs of PPHN is recommended after birth.

PACEF Recommendation
SSRIs should not be used in pregnancy unless the potential benefit outweighs the risk. The risk of neonatal withdrawal symptoms is highlighted by manufacturers, particularly if used during the third trimester. Fluoxetine and paroxetine have been identified as particular problems. Similarly SNRIs, such as venlafaxine and duloxetine, should be avoided in pregnancy unless the potential benefit outweighs the risk; withdrawal effects are a risk in neonates.

Antidepressants: risk of fractures

- Healthcare professionals should be aware of epidemiological data showing a small increased risk of bone fractures associated with the use of tricyclic antidepressants (TCAs) and SSRIs in patients aged 50 and over and should take risk into account in their discussions with patients and in prescribing decisions.
- From the available data, no definite conclusions can be drawn regarding dose-response, time relation and the underlying mechanism.

Oral tacrolimus products: measures to reduce risk of medication errors

- There are currently three different formulations of tacrolimus; they are not interchangeable (i.e. tacrolimus capsules (Prograf), tacrolimus prolonged release capsules (Advagraf Prolonged Release) and tacrolimus granules for oral suspension (Modigraf)). The launch of a fourth oral immediate release tacrolimus product, known as Adoport capsules, is imminent.

- By the end of February 2010, the MHRA had received 12 case reports involving prescribing/dispensing errors related to oral tacrolimus. These included four cases of acute rejection reaction, three cases of increased drug levels and two cases of increased creatinine.

Advice for healthcare professionals:

- To minimise medication errors arising from different formulations of tacrolimus, prescribers should either:
  provide full information, stating on the prescription the drug, exact form (capsules or granules; immediate release or prolonged release), strength, dose and dose frequency
  or:
  prescribe by brand name and include the strength, dose and dose frequency.
- Pharmacists should always dispense the exact pharmaceutical form and strength or brand and strength of oral tacrolimus that has been prescribed and should contact the prescriber if the prescriber's intention is not clear.
- Switching between tacrolimus formulations requires careful medical supervision and therapeutic monitoring under the supervision of a transplant specialist. Unsupervised switching can lead to under-dosing or overdosing of tacrolimus and risks transplant rejection or adverse reactions.
- Patients should take careful note of the name of their tacrolimus medicine and the dose and should check with their doctor or pharmacist if they receive an unfamiliar alternative or have questions about the dose.

PACEF Recommendation:
To date PACEF are aware of two incidents related to prescribing/dispensing errors with oral tacrolimus that have occurred in Lincolnshire. Prescribers should ensure that all prescribing of tacrolimus preparations is by brand name to avoid confusion. Pharmacists should be clear on the brand to be supplied against all prescriptions for tacrolimus. All existing patients on unlicensed tacrolimus 'specials' should be reviewed and, where possible, transferred to tacrolimus granules (Modigraf). The transfer of patients from any unlicensed treatment to Modigraf should be closely supervised by a transplant specialist. Tacrolimus capsules (Prograf), modified release capsules (Advagraf) and granules (Modigraf) are all designated AMBER requiring specialist initiation and appropriate shared care arrangements.

Acknowlegements

Many thanks to Cathy Johnson, Interface Lead Pharmacist, NHSL and Robyn Thompson, Senior Pharmacist, ULHT for their contributions to this edition of the *PACE Bulletin*.

June 2010