Greater East Midlands Commissioning Support Unit in association with
Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services,
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Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 8; Number 6 **March 2014**

What's new this month?

- **Following a review of safety and effectiveness, minocycline in all formulations is no longer recommended as a treatment for acne; it is designated RED-RED for this indication and has been removed from the *Lincolnshire Joint Formulary.* Lymecycline 408mg capsules are recommended as the preferred alternative; designation GREEN. Minocycline retains a limited unlicensed role in the treatment of atypical mycobacterial infections and folliculitis de calvans. For these indications, it is classed as RED (i.e. for hospital use only); all new initiations, with all prescribing and the associated monitoring, will be undertaken by the ULH Dermatology Service (see page 2).**
- **Aripiprazole prolonged-release suspension for injection (*Abilify Maintena*) has been approved for use within LPFT; designation RED. It has not been approved for prescribing within primary care (see page 4).**
- **PACEF have been working with LPFT colleagues to secure improved commissioning and supply arrangements for the prescribing of all depot antipsychotic injections for Lincolnshire patients. At present, work is ongoing to secure supply and administration of all depot antipsychotics through LPFTs community mental health teams. Until this new service is launched it would be appreciated if GPs could continue to prescribe depot antipsychotics for existing patients as an interim arrangement. All new initiations of antipsychotic depot injections are now the responsibility of LPFT (see page 5).**
- **A recent study has raised concerns over sub-optimal management of gout linked to relatively low rates of use of urate lowering therapy (ULT). Early treatment with ULT is known to reduce further crystal deposition and complications such as subcutaneous tophi and joint damage. PACEF issued guidance on the management of gout in April 2013 which encouraged the use of ULT and treatment to target urate levels. Prescribers are reminded that allopurinol should be started after two or more attacks of gout within a year or after the first attack in people at higher risk with one or more tophi, X-ray features of gouty arthritis, renal impairment, known uric acid stones or on long-term diuretic medication. Steps should also be taken to support patient adherence with treatment (see page 5).**
- **A recent meta-analysis provides further evidence of an increased risk of myocardial infarction with dabigatran compared to warfarin (see page 5).**

CONTENTS

– updated warnings and monitoring guidance; Capecitabine – Risk of severe skin reactions – discontinue treatment

SUMMARY OF PACEF DECISIONS: *FEBRUARY 2014 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Aripiprazole prolonged-release suspension for injection (*Abilify Maintena*)	For the maintenance treatment of patients with schizophrenia	RED. For use within LPFT only. Approved for inclusion on the *Lincolnshire Joint Formulary* for this indication.
Lymecycline 408mg capsules (*Tetralysal*)	For acne	GREEN. Already available on the *Lincolnshire Joint Formulary*.
Minocycline 50mg and 100mg capsules (generic/ *Aknemin/ Sebomin*)	For acne.	RED-RED for acne. Removed from the *Lincolnshire Joint Formulary* for this indication. N.B. Minocycline will continue to be used by ULH Dermatology for atypical mycobacterial infections and folliculitis decalvans; designation RED.
Minocycline 50mg and 100mg tablets (generic/ *Blemix/ Cyclomin/ Minocin/ Minogal*)	For acne	RED-RED for acne. Removed from the *Lincolnshire Joint Formulary* for this indication. N.B. Minocycline will continue to be used by ULH Dermatology for atypical mycobacterial infections and folliculitis decalvans; designation RED.
Minocycline modified release 100mg capsules (generic/ Acnamino/ *Minocin MR/ Sebren MR*)	For acne	RED-RED for acne. Removed from the *Lincolnshire Joint Formulary* for this indication. N.B. Minocycline will continue to be used by ULH Dermatology for atypical mycobacterial infections and folliculitis decalvans; designation RED.

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 in Lincolnshire website (www.lincolnshire.nhs.uk); follow the commissioning link to PACEF. Electronic copies of both the *PACE Bulletin* and our sister publication *PACE Shorts* (a short summary of the *PACE Bulletin*) are circulated to a wide readership via email. If you are not currently on our distribution list and wish to receive regular copies of PACEF publications please contact Sandra France on sandra.france@gemcsu.nhs.uk.

The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

GOODBYE TO MINOCYCLINE?

Last year, the *Drug and Therapeutics Bulletin* highlighted the risk to patients of continuing use of minocycline in the treatment of acne despite safety concerns that were first reported in the mid-1990s. The rare, but serious, side effects attributed to minocycline include the hypersensitivity reactions of eosinophilia, pneumonitis and nephritis, autoimmune hepatitis and lupus erythematosus-like syndrome. These reactions are more common with minocycline than with any other tetracycline. In addition, minocycline appears to be the only tetracycline that can cause potentially irreversible slate-grey pigmentation of the skin.

As well as these well-documented safety concerns, minocycline does not have any significant clinical advantages over other tetracyclines in the treatment of acne. Between tetracyclines, there is no difference in long-term outcome, no benefit of one agent over

another in acne resistant to other therapies and no evidence that the effects of minocycline last longer than other treatments.

In the face of such overwhelming evidence, many practices in Lincolnshire have reviewed their use of minocycline for acne in recent years and prescribing volume has markedly declined. Nonetheless, minocycline continues to be prescribed for this indication for some patients, with all four Lincolnshire CCGs showing some prescribing in primary care.

PACEF have reviewed the use of minocycline for acne with ULH dermatologists and have agreed the following:

- Minocycline should not be used for the treatment of acne; it will be removed from the *Lincolnshire Joint Formulary* and designated RED-RED for this indication.
- Existing patients should be reviewed and switched to lymecycline as a first preference assuming that they have not received this treatment before and have no contraindications.
- Where lymecycline is deemed to be inappropriate, the ULH Dermatology Service is willing to offer advice to GPs around possible alternatives on a case by case basis.
- No new patients should be initiated on minocycline for acne.
- Minocycline remains an appropriate treatment for atypical mycobacterial infections and folliculitis decalvans. For these unlicensed indications, minocycline will be classed as RED (i.e. for hospital use only) and all new initiations, with all prescribing and the associated monitoring, will be undertaken by the ULH Dermatology Service.

The table below details the range of tetracyclines available, equivalent doses and comparative costs:

	Licensed dose for acne	**28 days**	**Effect of food / milk**
Minocycline MR capsules 100mg (Minocin MR & other brands)	100mg one daily	£10.04	Absorption is not significantly impaired by food affected by food or moderate amounts of milk
Minocycline 50mg capsules	50mg twice daily	£15.27	
Minocycline 100mg capsules	100mg once daily	£13.09	
Minocycline 50mg tablets	50mg twice daily	£11.36	
Minocycline 100mg tablets	100mg once daily	£12.38	
Lymecycline 408mg capsules	408mg once daily	£6.22	Absorption is not affected by moderate amounts of milk
Oxytetracycline 250mg tablets	500mg twice daily	£4.80	Take on an empty stomach, one hour before or 2 hours after food.
Tetracycline 250mg tablets	500mg twice daily	£12.12	
Doxycycline 100mg capsules	100mg once daily	£3.89	Absorption not significantly affected by food or milk; if gastric irritation occurs take after food.

Prices: *Drug Tariff* (January 2014)

PACEF Recommendation:

Following a review of safety and effectiveness, minocycline in all formulations is no longer recommended as a treatment for acne; it is designated RED-RED for this indication and has been removed from the *Lincolnshire Joint Formulary.* Lymecycline 408mg capsules are recommended as the preferred alternative; designation GREEN. Minocycline retains a limited unlicensed role in the treatment of atypical mycobacterial infections and folliculitis decalvans. For these indications, it is classed

as RED (i.e. for hospital use only); all new initiations, with all prescribing and the associated monitoring, will be undertaken by the ULH Dermatology Service

Reference:
'Time to say goodbye to minocycline?', *Drug and Therapeutics Bulletin*, May 2013; 51(5):48.

NEW FORMULATION ASSESSMENT: *ARIPIPRAZOLE PROLONGED-RELEASE SUSPENSION FOR INJECTION (ABILIFY MAINTENA)*

Aripiprazole prolonged-release suspension for injection (*Abilify Maintena*) is a long-acting injection formulation of the active substance aripiprazole. It is indicated for the maintenance treatment of schizophrenia in adults already stabilized on oral aripiprazole.

The recommended starting dose of 400mg into the gluteal muscle is also the maintenance dose, every month; dose reduction to 300mg can be considered for those intolerant of the intial dose.

PACEF reviewed one study involving adults whose disease had already been stabilized on oral aripiprazole. In a comparison of oral aripiprazole with *Abilify Maintena*, 22 out of the 265 patients (8.3%) treated with *Abilify Maintena* saw symptoms recur within 26 weeks compared to 21 out of 266 (7.9%) patients treated with oral aripiprazole. From this, it can be concluded that *Abilify Maintena* is non-inferior to oral aripiprazole in terms of prevention of the return of the symptoms. This position has also been accepted by the European Committee for Medicinal Products for Human Use (CHMP); they concluded that *Abilify Maintena* is as effective as oral aripiprazole with a similar safety profile with the exception of injection pain, which was considered manageable. They also concluded that monthly administration may help patients to adhere to their treatment.

The efficacy of *Abilify Maintena* in the maintenance treatment of patients with schizophrenia was established in two randomised, double-blind trials. The pivotal trial was a 38 week, RCT in 662 patients designed to establish the efficacy, safety, and tolerability of monthly injections compared to once daily oral aripiprazole tablets 10-30 mg in adult patients with schizophrenia. The primary endpoint again demonstrated that 400 mg and 300 mg of *Abilify Maintena* was non-inferior to aripiprazole oral tablets 10-30 mg. The relapse rate by end of week 26 was 7.12 % in the long-acting injection group, and 7.76 % in the oral aripiprazole tablets 10-30 mg group.

A cost comparison between aripiprazole oral tablets and aripiprazole prolonged release suspension for injection (*Abilify Maintena*) reveals the following:

	Maintenance dose for schizophrenia	Cost 28 days
Aripiprazole 10mg tablets (*Abilify*)	10mg once daily	£96.04
Aripiprazole 15mg tablets (*Abilify*)	15mg once daily	£96.04
Aripiprazole 30mg tablets (*Abilify*)	30mg once daily	£192.08
Aripiprazole 400mg prolonged release suspension for injection (*Abilify Maintena*)	400mg once a month	£220.41
Risperidone 25mg sustained release injection (*Risperdal Consta*)	25mg every 2 weeks	£159.38
Risperidone 37.5mg sustained release injection (*Risperdal Consta*)	37.5mg every 2 weeks	£222.64
Risperidone 50mg sustained release injection (*Risperdal Consta*)	50mg every 2 weeks	£285.52

PACEF Recommendation:
Aripiprazole prolonged release suspension for injection (*Abilify Maintena*) is approved for use within LPFT and designated RED. It will be added to the *Lincolnshire Joint Formulary* for the maintenance treatment of patients with schizophrenia. *Abilify Maintena* is likely to be used within LPFT as an alternative to risperidone sustained release injection (*Risperdal Consta*) as it has only one standard dose, does not need to be stored in the refrigerator prior to use and the two products are comparably priced. *Abilify Maintena* has not been approved for prescribing in primary care.

UPDATE ON REVISED COMMISSIONING ARRANGEMENTS FOR DEPOT ANTIPSYCHOTIC DRUGS

PACEF have been working with LPFT colleagues to secure improved commissioning and supply arrangements for the prescribing of all depot antipsychotic injections for Lincolnshire patients. At present, work is ongoing to secure supply and administration of all depot antipsychotics through LPFTs community mental health teams. Until this new service is launched it would be appreciated if GPs could continue to prescribe depot antipsychotics for existing patients as an interim arrangement. All new initiations of antipsychotic depot injections are now the responsibility of LPFT.

NEW TRIAL ASSESSMENTS

GOUT INCREASING BUT URATE LOWERING THERAPIES STILL UNDER-USED

Using UK practice data from the Clinical Practice Research Datalink trends in the burden and management of gout from 1997 to 2012 were assessed. Both the prevalence and incidence of gout increased over the study period (by 63.9% and 29.6% respectively) with a prevalence of 2.49% and incidence of 1.77 per 1000 person-years in 2012. The proportion of people treated with urate lowering therapies (ULT) did not change during the study period (approximately 38% in existing cases), although adherence to ULT improved from 28% in 1997 to 39% in 2012.

PACEF Comment:
The authors suggest that rates of use of ULT are low and reflect sub-optimal management of gout. Early treatment with ULT is known to reduce further crystal deposition and complications such as subcutaneous tophi and joint damage. PACEF issued guidance on the management of gout in *PACE Bulletin* Vol 7 No 10 (April 2013); this includes information on treating people to a target urate level and managing people with renal impairment. PACEF are intending to produce a second edition of the *Gout Treatment Algorithm* to reflect changes suggested by this study. Specifically, allopurinol should be started after two or more attacks of gout within a year or after the first attack in people at higher risk with one or more tophi, X-ray features of gouty arthritis, renal impairment, known uric acid stones or on long-term diuretic medication. Steps should also be taken to support patient adherence with treatment.

Reference:
Kuo CF et al., Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Annals of Rheumatic Disease* published early online Jan 15 2014 doi: 10.1136/annrheumdis-2013-204463

ORAL DIRECT THROMBIN INHIBITORS AND THE RISK OF MYOCARDIAL INFARCTION

In a meta-analysis of eleven randomized controlled trials (n=39,357), the oral direct thrombin inhibitors, dabigatran and ximelagatran, were compared with warfarin for any indication where the occurrence of MI was reported. Four of the RCTs involved dabigatran (n=23,757),

5 involved ximelagatran and 2 involved a drug still in development. Overall, oral direct thrombin inhibitors were associated with a statistically significant increased risk of MI compared with warfarin. The authors calculate an absolute increase in risk of 0.53% over 3 – 24 months and a number needed to harm of 188.

PACEF Comment:
Prescribers are reminded that dabigatran (*Pradaxa*) is currently the only oral direct thrombin inhibitor available in the UK. The other newer oral anticoagulants apixaban and rivaroxaban, are direct factor Xa inhibitors working on a different part of the coagulation cascade. The RE-LY study compared dabigatran with warfarin in 18,113 people with atrial fibrillation and found an overall higher rate of MI with dabigatran in comparison to warfarin. This meta-analysis suggests that the increased risk of MI is likely to be a class effect involving all oral direct thrombin inhibitors. There are a number of limitations to the data, principally that MI was not a pre-specified outcome and the conclusions are heavily weighted by data derived from RE-LY. Nonetheless, prescribers need to be aware that the risk of MI with dabigatran is higher than that with warfarin and that the absolute risk of MI is higher in patients with previous MI, patients ≥ 65 years with either diabetes or coronary artery disease, patients with left ventricular ejection fraction < 40 %, and patients with moderate renal dysfunction. Furthermore, a higher risk of MI was also seen in patients taking concomitant antiplatelet therapy. Prescribers should consider this possible increased risk when choosing anticoagulant treatments for their patients.

Reference: Artang R et al, Meta-analysis of randomized controlled trials on risk of myocardial infarction from the use of oral direct thrombin inhibitors. *Am J Cardiol* 2013 Dec 15: 112 (12): 1973-9.

MEDICINES AND HEALTHCARE REGULATORY AGENCY: *DRUG SAFETY UPDATE* (JANUARY 2014)

PRASUGREL (EFIENT): INCREASED RISK OF BLEEDING – INFORMATION ON TIMING OF LOADING DOSE

New clinical trial information is available on the timing of the loading dose of prasugrel when used in patients with unstable angina or non-ST segment elevation myocardial infarction. In these patients, when coronary angiography is done within 48 hours after admission, the loading dose should only be given at the time of percutaneous coronary intervention.

Advice for healthcare professionals is as follows:

- Prasugrel is approved as a single 60mg loading dose (followed by a maintenance dose of 5 to 10mg daily recommended for up to 1 year); this remains unchanged.
- Patients with unstable angina or NSTEMI, who undergo coronary angiography within 48 hours of admission, should be given a loading dose of 60mg at the time of PCI only, to minimise bleeding risk.

OFATUMUMAB: SCREEN FOR HEPATITIS B VIRUS BEFORE TREATMENT

All patients should be screened for hepatitis B virus infection before starting treatment with ofatumumab. Patients with active infection with this virus should not be treated with ofatumumab. Those with positive hepatitis B serology should be referred to a specialist in liver disease for consultation about monitoring and initiation of antiviral treatment. If reactivation of hepatitis B virus occurs, ofatumumab and any concomitant chemotherapy should be interrupted immediately, and appropriate treatment instituted.

Advice for healthcare professionals:

- All patients should be screened for hepatitis B virus infection before starting treatment with ofatumumab
- Patients with active hepatitis B infection should not be treated with ofatumumab
- Patients with positive hepatitis B serology (but no active disease) should be referred to a specialist in liver disease for consultation about monitoring and initiation of antiviral treatment for hepatitis B before starting treatment with ofatumumab
- If reactivation of hepatitis B virus occurs, ofatumumab and any concomitant chemotherapy should be interrupted immediately, and appropriate treatment instituted

PACEF Comment:
Ofatumumab infusion (*Arzerra*) has an extremely limited role. It is only approved for use in Lincolnshire in accordance with National Cancer Drugs Fund List criteria for the treatment of chronic lymphocytic leukaemia. NICE did not approve the product for use for this indication in TA202 published in October 2010. It is expected that pre-treatment screening for hepatitis B would be the responsibility of the secondary or tertiary care centre treating the patient.

TEMOZOLOMIDE: RISK OF HEPATIC INJURY, INCLUDING FATAL HEPATIC FAILURE – UPDATED WARNINGS AND MONITORING GUIDANCE

Hepatic injury, including hepatic failure with fatal outcome, has been reported in patients treated with temozolomide. Liver function should be tested before and during treatment. Physicians should carefully consider the benefits of continuing treatment versus the risk of potentially severe liver injury if patients develop significant liver function abnormalities.

Advice for healthcare professionals:

- Baseline LFTs should be done before starting temozolomide treatment. If these tests are abnormal, physicians should consider the balance of benefits and risks when deciding whether to start treatment
- Patients on a 42-day treatment cycle should have LFTs repeated midway through this cycle. All patients should have LFTs checked after every treatment cycle
- If a patient develops significantly abnormal LFTs, the benefits of continuing treatment should be carefully considered versus the risk of potentially severe liver toxicity.
- Liver toxicity may occur several weeks or more after initiation of treatment or after the last treatment with temozolomide

PACEF comment
Temozolomide capsules (*Temodal*) have been approved by NICE for the treatment of recurrent malignant glioma (brain cancer) which has not responded to first-line chemotherapy; designation RED (see NICE TA23 (April 2001). It is expected that all monitoring of LFTs would be the responsibility of the secondary or tertiary care centre treating the patient.

CAPECITABINE: RISK OF SEVERE SKIN REACTIONS – DISCONTINUE TREATMENT

Severe skin reactions such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported during treatment with capecitabine. Some cases were fatal. Capecitabine should be discontinued if a serious skin reaction occurs, and the reaction should be treated promptly.

Advice for healthcare professionals:

- TEN and SJS are characterised by generalised tender erythematous maculae, progressing to blisters and denudation and commonly preceded by photophobia, symptoms of upper respiratory tract infection, and fever.
- Patients should be informed of the possibility of such reactions and informed to seek urgent medical advice should any symptoms of a severe skin reaction occur.
- Capecitabine should be permanently discontinued in patients who have a severe skin reaction during treatment; the reaction should be treated promptly

PACEF comment

Capecitabine tablets (*Xeloda*) are recommended by NICE for a range of different cancers including stage III colon cancer, metastatic colon cancer and advanced gastric cancer. Capecitabine is approved for use on the *Lincolnshire Joint Formulary* and is designated RED. Whilst no prescribing is expected within primary care, patients may seek advice from their GP if suffering from one of the skin reactions detailed above.

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