Arden and Greater East Midlands
Commissioning Support Unit

Greater East Midlands Commissioning Support Unit in association with
Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services,
United Lincolnshire Hospitals Trust and Lincolnshire Partnership Foundation Trust

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 9; Number 2 **February 2015**

What's new this month?

- **Low cost generic standard release quetiapine tablets remain the preferred first line option in most patients where quetiapine is clinically indicated. However, lower cost modified release brands of quetiapine are now available and should be preferred in patients requiring a modified release product. The lower cost brands approved by PACEF and included in the *Lincolnshire Joint Formulary* are *Ebesque XL*, *Biquelle XL* and *Zaluron XL*; of these, *Biquelle XL* and *Zaluron XL* are the lowest cost. All of these products are designated GREEN in all strengths. Practices currently prescribing higher cost modified release quetiapine preparations are urged to review their position with a view to switching to their preferred lower cost brand. Lower cost MR quetiapine should be prescribed by brand name to ensure a lower NHS reimbursement price is paid. Practices are advised not to issue open generic prescriptions for quetiapine MR or to issue branded prescriptions for higher cost products such as *Seroquel XL*, *Seotiapim XL*, *Sondate XL*, and *Tenprolide XL*. All of these products are designated RED-RED and none are included on the *Lincolnshire Joint Formulary* (see page 3).**
- **As the only anticholinergic with a marketing authorisation for hyperhidrosis, propantheline 15mg tablets (*Pro-Banthine*) are approved for use for this indication, designated AMBER without shared care (see page 6).**
- **Fusidic acid 2% cream (*Fucidin Cream*) and sodium fusidate 2% ointment (*Fucidin Ointment*) are designated GREEN for the treatment of limited first episode impetigo only. Systemic flucloxacillin remains the recommended treatment of choice for infected eczema (see page 7).**
- **NICE have approved nalmefene (*Selincro*) to reduce alcohol consumption in those with a high drinking risk level. Trial evidence suggests that the potential benefits of nalmefene in these patients are dependent upon initial evaluation using a two week alcohol consumption diary, followed by continuous psychosocial support focused on treatment adherence and reduction of alcohol consumption for those that end up on prescribed therapy. As this level of support is only available through specialist alcohol services, nalmefene tablets 18mg (*Selincro*) are only approved for restricted use within the *Lincolnshire Joint Formulary* and are designated RED. Primary care clinicians are encouraged to undertake opportunistic screening for alcohol use disorders using the Alcohol Use Disorders Identification Test (AUDIT); referral to specialist services is recommended for all patients scoring 20-40 (see page 9).**
- **Potassium permanganate in any formulation is for external use only and can be fatal if ingested orally due to local inflammatory reactions that block the airways or cause perforation of the gastro-intestinal tract. The National Reporting and Learning System (NRLS) has identified 43 incidents in the last three and a half years where potassium permanganate tablets have been ingested orally by patients. In one incident reported in Lincolnshire, a non-English speaking patient misunderstood instructions for use. As the risk of error seems to increase when the term potassium permanganate tablets is used, consideration should be given to using the term potassium permanganate soak on dispensed labels and in patient notes. Care should be taken to ensure that the patient is fully aware of how to use potassium permanganate tablets and realises that the product is for external use only. Particular care should be taken when prescribing and dispensing potassium permanganate tablets to vulnerable patients in their own**

homes. If accidental ingestion occurs, it must be treated as a medical emergency (see page 11).

CONTENTS

SUMMARY OF PACEF DECISIONS: *JANUARY 2015 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Darbepoetin alfa (*Aranesp*) pre-filled syringe (Amgen)	Anaemia associated with chronic renal failure and in adults with non-myeloid malignancies receiving chemotherapy.	Subcutaneous injection is designated AMBER with shared care and intravenous injection RED. Restricted for use in haematology and renal services only. Included in the *Lincolnshire Joint Formulary* for this indication.
Epoetin alfa (*Eprex*) pre-filled syringe (Jannsen-Cilag)	Anaemia associated with chronic renal failure including dialysis patients. Anaemia and reduction of transfusions in adults receiving chemotherapy for solid tumour, malignant lymphoma or multiple myeloma	Subcutaneous injection is designated AMBER with shared care and intravenous injection RED. Restricted for use in haematology and renal services only. Included in the *Lincolnshire Joint Formulary* for this indication.
Epoetin beta (*NeoRecormon*) pre-filled syringe (Roche)	Anaemia associated with chronic renal failure including dialysis patients. Anaemia in adults with non-myeloid malignancies receiving chemotherapy.	Subcutaneous injection is designated AMBER with shared care and intravenous injection RED. Restricted for use in haematology and renal services only. Included in the *Lincolnshire Joint Formulary* for this indication.
Fusidic acid 2% cream (*Fucidin Cream*) (Leo)	Bacterial skin infections	GREEN for the treatment of limited first episode impetigo only. Systemic flucloxacillin remains the recommended treatment of choice for infected eczema. Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Imatinib tablets 400mg (*Glivec*) (Novartis)	Gastro-intestinal stromal tumours	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Nalmefene tablets 18mg (*Selincro*) (Lundbeck)	For the reduction of alcohol consumption in adult patients	RED Approved for restricted use within

	with alcohol dependence who have a high drinking risk level without physical withdrawal symptoms and who do not need immediate detoxification.	**specialist alcohol services only. Included in the *Lincolnshire Joint Formulary.***
Propantheline 15mg tablets *(Pro-Banthine)*	**Hyperhidrosis**	**AMBER without shared care. Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.**
Quetiapine MR tablets 50mg, 150mg, 200mg, 300mg and 400mg (*Biquelle XL*) (Aspire Pharma)	**For the treatment of schizophrenia, bipolar disorder and add-on treatment of major depressive episodes in patients with major depressive disorder**	**GREEN Approved for inclusion in the *Lincolnshire Joint Formulary.* Prescribe by brand. Standard release quetiapine preferred first line.**
Quetiapine modified release tablets 50mg, 200mg, 300mg and 400mg (*Ebesque XL*) (DB Ashbourne)	**For the treatment of schizophrenia, bipolar disorder and add-on treatment of major depressive episodes in patients with major depressive disorder**	**GREEN Approved for inclusion in the *Lincolnshire Joint Formulary.* Prescribe by brand. Standard release quetiapine preferred first line.**
Quetiapine MR tablets 50mg, 150mg, 200mg, 300mg and 400mg (*Zaluron XL*) (Fontus Health)	**For the treatment of schizophrenia, bipolar disorder and add-on treatment of major depressive episodes in patients with major depressive disorder**	**GREEN Approved for inclusion in the *Lincolnshire Joint Formulary.* Prescribe by brand. Standard release quetiapine preferred first line.**
Sodium fusidate 2% ointment (*Fucidin Ointment*) (Leo)	**Bacterial skin infections**	**GREEN for the treatment of limited first episode impetigo only. Systemic flucloxacillin remains the recommended treatment of choice for infected eczema. Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.**

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 PACEF website (http://lincolnshire-pacef.nhs.uk); follow the commissioning link to PACEF. Electronic copies 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.

Google searching can be a quick and effective way of finding back numbers of the *PACE Bulletin* relevant to a specific topic of interest. Searchers are advised to use the official version of the *Bulletin* available from the PACEF website rather than depend on a potentially unreliable draft or variant found through Google or an alternative search engine.
The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

RAPID DRUG ASSESSMENT: *QUETIAPINE MODIFIED RELEASE FORMULATIONS*

A number of new modified release quetiapine formulations are in the process of being launched into the UK marketplace. All of these products are bioequivalent with *Seroquel XL* and some are priced at 50% lower than the originator brand. Among the new lower cost products are *Ebesque XL* (DB Ashbourne), *Biquelle XL* (Aspire Pharma Ltd) and *Zaluron XL* (Fontus Health Ltd).

Current PACEF advice is to prescribe quetiapine as the standard release generic. Since our last published assessment, the generic reimbursement price of standard release quetiapine has fallen even further. Practices have been encouraged and supported to implement therapeutic switches from modified release quetiapine to the equivalent dose standard release generic. However, while some practices have been willing to undertake this switch, others have expressed unease about implementation without endorsement from the initiating specialist. In many cases, patients stabilised on long-term quetiapine have been discharged

from specialist support and it has been difficult to find an initiating psychiatrist to support such a switch. After reviewing a range of new lower cost MR products, PACEF are in support of therapeutic switching from *Seroquel XL* to one of the approved lower cost MR brands as an alternative to the switch to standard release generic quetiapine. The QIPP savings will not be as great, but such a switch would reduce prescribing costs by 50%. The table below illustrates the cost differential. Lower cost products are highlighted in bold.

	Dose	**Cost (30 days)**
Quetiapine tablets 25mg (generic)	**25mg twice daily**	**£1.44**
Quetiapine tablets 25mg (*Seroquel*) (AstraZeneca)	25mg twice daily	£40.50
Quetiapine MR tablets 50mg (*Seroquel XL*) (AstraZeneca)	50mg once daily	£33.83
Quetiapine MR tablets 50mg (*Atrolak XL*) (Accord Healthcare)	50mg once daily	£32.14
Quetiapine MR tablets 50mg (*Biquelle XL*) (Aspire Pharma)	**50mg once daily**	**£14.73**
Quetiapine MR tablets 50mg (*Ebesque XL*) (DB Ashbourne)	**50mg once daily**	**£19.92**
Quetiapine MR tablets 50mg (*Sondate XL*) (Teva UK)	50mg once daily	£32.00
Quetiapine MR tablets 50mg (*Tenprolide XL*) (Actavis UK)	50mg once daily	£33.83
Quetiapine MR tablets 50mg (*Zaluron XL*) (Fontus Health)	**50mg once daily**	**£14.73**
Quetiapine tablets 25mg (generic)	**50mg twice daily**	**£2.88**
Quetiapine tablets 25mg (*Seroquel*)	50mg twice daily	£81.00
Quetiapine tablets 100mg (generic)	**100mg twice daily**	**£2.37**
Quetiapine tablets 100mg (*Seroquel*) (AstraZeneca)	100mg twice daily	£113.10
Quetiapine MR tablets 200mg (*Seroquel XL*) (AstraZeneca)	200mg once daily	£56.55
Quetiapine MR tablets 200mg (*Atrolak XL*) (Accord Healthcare)	200mg once daily	£53.73
Quetiapine MR tablets 200mg (*Biquelle XL*) (Aspire Pharma)	**200mg once daily**	**£24.73**
Quetiapine MR tablets 200mg (*Ebesque XL*) (DB Ashbourne)	**200mg once daily**	**£28.28**
Quetiapine MR tablets 200mg (*Seotiapim XL*) (Sandoz)	200mg once daily	£48.07
Quetiapine MR tablets 200mg (*Sondate XL*) (Teva UK)	200mg once daily	£53.73
Quetiapine MR tablets 200mg (*Tenprolide XL*) (Actavis UK)	200mg once daily	£56.55
Quetiapine MR tablets 200mg (*Zaluron XL*) (Fontus Health)	**200mg once daily**	**£24.73**
Quetiapine tablets 150mg (generic)	**150mg twice daily**	**£2.81**
Quetiapine tablets 150mg (*Seroquel*) (AstraZeneca)	150mg twice daily	£113.10
Quetiapine MR tablets 300mg (*Seroquel XL*) (AstraZeneca)	300mg once daily	£85.00
Quetiapine MR tablets 300mg (*Biquelle XL*) (Aspire Pharma)	**300mg once daily**	**£37.23**
Quetiapine MR tablets 300mg (*Ebesque XL*) (DB Ashbourne)	**300mg once daily**	**£42.50**
Quetiapine MR tablets 300mg (*Seotiapim XL*) (Sandoz)	300mg once daily	£72.25
Quetiapine MR tablets 300mg (*Sondate XL*) (Teva UK)	300mg once daily	£80.75
Quetiapine MR tablets 300mg (*Tenprolide XL*) (Actavis UK)	300mg once daily	£85.00
Quetiapine MR tablets 300mg (*Zaluron XL*) (Fontus Health)	**300mg once daily**	**£37.23**
Quetiapine tablets 200mg	**200mg twice daily**	**£3.10**

(generic)		
Quetiapine tablets 200mg (*Seroquel*) (AstraZeneca)	200mg twice daily	£113.10
Quetiapine MR tablets 400mg (*Seroquel XL*) (AstraZeneca)	400mg once daily	£113.10
Quetiapine MR tablets 400mg (*Biquelle XL*) (Aspire Pharma)	**400mg once daily**	**£49.48**
Quetiapine MR tablets 400mg (*Ebesque XL*) (DB Ashbourne)	**400mg once daily**	**£56.55**
Quetiapine MR tablets 400mg (*Seotiapim XL*) (Sandoz)	400mg once daily	£96.14
Quetiapine MR tablets 400mg (*Sondate XL*) (Teva UK)	400mg once daily	£120.95
Quetiapine MR tablets 400mg (*Tenprolide XL*) (Actavis UK)	400mg once daily	£113.10
Quetiapine MR tablets 400mg (*Zaluron XL*) (Fontus Health)	**400mg once daily**	**£49.48**
Quetiapine tablets 300mg (generic)	**300mg twice daily**	**£4.40**
Quetiapine tablets 300mg (*Seroquel*)	300mg twice daily	£170.00

From this comparison, three products emerge as lower cost: *Ebesque XL*, *Biquelle XL* and *Zaluron XL*; of these, *Biquelle XL* and *Zaluron XL* are the lowest cost.

Potential Cost Saving: *Modified Release Quetiapine to Standard Release Quetiapine*

Therapeutic switching from modified release quetiapine to generic standard release quetiapine has the potential to generate significant savings across the Lincolnshire CCGs:

CCG	**Annual 100% saving**
Lincolnshire East CCG	£148,278
Lincolnshire West CCG	£353,040
South Lincolnshire CCG	£48,006
South West Lincolnshire CCG	£40,194
Lincolnshire	£589,518

Potential Cost Saving: *Modified Release Quetiapine to Quetiapine fumarate sustained release tablets (Ebesque XL)*

Where this is problematic or impractical, therapeutic switching from a higher cost modified release quetiapine formulation (e.g. *Seroquel XL*) to a lower cost preferred MR brand has the potential to generate lower, but still significant savings.

CCG	**Annual 100% saving**
Lincolnshire East CCG	£78,041
Lincolnshire West CCG	£185,811
South Lincolnshire CCG	£25,266
South West Lincolnshire CCG	£21,155
Lincolnshire	£310,273

These figures assume that patients taking *Seroquel XL* are switched to *Ebesque XL*; savings would be even greater if one of the two even lower cost products (*Biquelle XL* or *Zaluron XL*) were used.

PACEF Recommendation:
Low cost generic standard release quetiapine tablets remain the preferred first line option in most patients where quetiapine is clinically indicated. However, lower cost modified release brands of quetiapine are now available and should be preferred in patients requiring a modified release product. The lower cost brands approved by PACEF and included in the *Lincolnshire Joint Formulary* are *Ebesque XL* (DB

Ashbourne), *Biquelle XL* (Aspire Pharma Ltd) and *Zaluron XL* (Fontus Health Ltd); of these, *Biquelle XL* and *Zaluron XL* are the lowest cost. All of these products are designated GREEN in all strengths. Practices currently prescribing higher cost modified release quetiapine preparations are urged to review their position with a view to switching to their preferred lower cost brand. Lower cost MR quetiapine should be prescribed by brand name to ensure a lower NHS reimbursement price is paid. Practices are advised not to issue open generic prescriptions for quetiapine MR or to issue branded prescriptions for higher cost products such as *Seroquel XL* (AstraZeneca), *Seotiapim XL* (Sandoz), *Sondate XL* (Teva UK), and *Tenprolide XL* (Actavis UK). All of these products are designated RED-RED and none are included on the *Lincolnshire Joint Formulary.*

RAPID DRUG ASSESSMENT: *PROPANTHELINE 15MG TABLETS (PRO-BANTHINE) FOR HYPERHIDROSIS*

Propantheline 15mg tablets (*Pro-Banthine*) are currently the only licensed oral treatment for hyperhidrosis. Published guidance on the management of hyperhidrosis from the International Hyperhidrosis Society recommends the use of oral antimuscarinics as a treatment option. NICE bemoan the lack of clinical trial evidence supporting the use of these agents for this indication, but recognise that specialist opinion is divided.

Hyperhidrosis or excessive sweating is linked to over activity of the sympathetic nervous system. There are three main types:

- Primary or focal hyperhidrosis is a common disorder affecting approximately 1% of the population. It commonly affects the palms, soles of the feet and the axillae.
- Generalised hyperhidrosis in a well patient with a classical history of sweating starting in late childhood and improving in middle age is seldom related to an underlying medical condition. If the patient is unwell or if sweats occur mainly at night then it is likely to be linked to a secondary cause (e.g. Parkinson's disease, thyroid disease, diabetes, lymphoma) or caused by medication (e.g. SSRI's, opioids, oestrogens).
- Gustatory hyperhidrosis is induced by food or drink and can be associated with diabetes.

The Primary Care Dermatology Society recommends that oral anticholinergics should be considered first line for the management of generalised hyperhidrosis. Propantheline is recommended as the only licensed product starting at an initial dose of 15mg once or twice a day and increasing according to response and tolerance. Modified release oxybutynin is a possible alternative, but is not licensed for this indication. Other treatments occasionally used include beta-blockers that cross the blood-brain barrier (e.g. propranolol 40 mg three times a day) or diltiazem (60 mg three times a day). .

The limiting factor on the use of anticholinergics for this, and indeed any, indication is the prevalence of adverse effects which can prove intolerable to some patients. In addition, propantheline, as an antimuscarinic, is also implicated in a number of drug interactions that can contraindicate its use in certain patient groups.

A cost comparison between propantheline 5mg tablets and alternative anticholinergic options reveals that propantheline is both the lowest cost and the only licensed option.

Drug	**Daily dose**	**Cost (£) 28 days**
Propantheline 15mg tablets (*Pro-Banthine*)	15mg three times daily	£15.55

Oxybutynin 10mg MR tablets (*Lyrinel XL*)	10mg daily	£25.70
Glycopyrronium bromide 2mg/5ml oral suspension	2mg up to three times daily	£654.43*

*Price based on 2mg/5ml oral suspension, unlicensed special part VIIIB *Drug Tariff*.

PACEF Recommendation
PACEF recognise the prominence of oral anticholinergics in a range of national and international guidelines defining best practice in the treatment of hyperhidrosis. As the only anticholinergic with a marketing authorisation for this indication, propantheline 15mg tablets (*Pro-Banthine*) are approved for use and designated AMBER without shared care. They are included in the *Lincolnshire Joint Formulary* for this indication. Although propantheline is also licensed for the treatment of GI disorders characterised by smooth muscle spasm and adult enuresis, it is only availabe on the *Formulary* for hyperhidrosis.

REVIEW OF FORMULARY STATUS OF TOPICAL SODIUM FUSIDATE

Despite the fact that fusidic acid 2% cream (*Fucidin Cream*) and sodium fusidate 2% ointment (*Fucidin Ointment*) are licensed for the treatment of bacterial skin infections, the products are restricted for use in very severe staphylococcal skin infections and have been designated RED. This decision was based on advice from microbiology that highlighted the risk that widespread use of topical fusidic acid would inevitably lead to increased resistance against systemic fusidic acid rendering it potentially ineffective against severe staphylococcal infections, such as osteomyelitis or systemic MRSA. This decision has caused some frustration among GPs and has failed to prevent significant ongoing prescribing of these products in Lincolnshire primary care despite the restricted status within the *Formulary*.

PACEF reviewed the Health Protection Agency guidelines on the management of infectious disease in primary care that recommend topical sodium fusidate for the treatment of very localised impetigo. After discussion with Dr Bethan Stoddart, ULH Consultant Microbiologist, it has been agreed that the *Formulary* entry for both products will be amended to read: GREEN for the treatment of limited first episode impetigo. Systemic flucloxacillin remains the recommended treatment for infected eczema.

PACEF Recommendation:
Fusidic acid 2% cream (*Fucidin Cream*) and sodium fusidate 2% ointment (*Fucidin Ointment*) are designated GREEN for the treatment of limited first episode impetigo only. Systemic flucloxacillin remains the recommended treatment of choice for infected eczema.

NICE TECHNOLOGY APPRAISAL 323: *ERYTHROPOIESIS STIMULATING AGENTS (EPOETIN AND DARBEPOETIN) FOR TREATING ANAEMIA IN PEOPLE WITH CANCER HAVING CHEMOTHERAPY* (NOVEMBER 2014)

Erythropoiesis-stimulating agents (epoetin alfa, beta, theta and zeta, and darbepoetin alfa) are recommended, within their marketing authorisations, as options for treating anaemia in people with cancer who are having chemotherapy.

If different erythropoiesis-stimulating agents are equally suitable, the product with the lowest acquisition cost for the course of treatment should be used.

Epoetin alfa, beta, theta and zeta are recombinant human erythropoietin analogues used to shorten the period of symptomatic anaemia in people having cytotoxic chemotherapy.

Epoetins are recommended for use when haemoglobin concentrations are 100 g/litre or lower, and target values up to 120 g/litre.

There are 2 brands of epoetin alfa, *Eprex* (Janssen‑Cilag) and *Binocrit* (Sandoz), and both have UK marketing authorisations for the 'treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, who are at risk of transfusion'. *Binocrit* is a biosimilar medicine referenced to *Eprex*.

Epoetin beta (*NeoRecormon*, Roche Products) has a UK marketing authorisation for the 'treatment of symptomatic anaemia in adult patients with non‑myeloid malignancies who are receiving chemotherapy'

Epoetin theta (*Eporatio*, Teva UK) has a UK marketing authorisation for the 'treatment of symptomatic anaemia in adult patients with non‑myeloid malignancies who are receiving chemotherapy'

Epoetin zeta (*Retacrit*, Hospira UK) is a biosimilar medicine referenced to *Eprex*. It has a UK marketing authorisation for the 'treatment of anaemia and reduction of transfusion requirements in adult patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma, who are at risk of transfusion'.

Darbepoetin alfa (*Aranesp*, Amgen) is a hyperglycosylated derivative of epoetin that stimulates erythropoiesis by the same mechanism as the endogenous hormone. *Aranesp* has a UK marketing authorisation for the 'treatment of symptomatic anaemia in adult cancer patients with non‑myeloid malignancies who are receiving chemotherapy'. The summary of product characteristics recommends that darbepoetin alfa should be used at haemoglobin concentrations of 100 g/litre or lower, with target values up to 120 g/litre.

PACEF Recommendation:
Epoetin alfa (*Eprex*) pre-filled syringe, darbepoetin alfa (*Aranesp*) pre-filled syringe and epoetin beta pre-filled syringe (*NeoRecormon*) are all approved for use through the *Lincolnshire Joint Formulary*. Subcutaneous injection is designated AMBER with shared care and intravenous injection RED. All three products are restricted for use in haematology and renal services only.

NICE TECHNOLOGY APPRAISAL 324: *DUAL-CHAMBER PACEMAKERS FOR SYMPTOMATIC BRADYCARDIA DUE TO SICK SINUS SYNDROME WITHOUT ATRIOVENTRICULAR BLOCK (NOVEMBER 2014)*

Dual-chamber pacemakers are recommended as an option for treating symptomatic bradycardia due to sick sinus syndrome without atrioventricular block.

Notes

The DANPACE study (2011) compared rate‑responsive dual‑chamber pacemakers (n=708) with rate‑responsive single‑chamber atrial pacemakers (n=707) in the treatment of sick sinus syndrome (including those with sino‑atrial block or sinus‑arrest, sinus bradycardia and bradycardia‑tachycardia). The study was based in Denmark, the UK and Canada with a mean follow‑up of 5.4 years. The primary outcome was death by any cause. Secondary outcomes included paroxysmal or chronic atrial fibrillation, stroke, cardiovascular mortality, need for pacemaker re‑operation and quality of life. The DANPACE trial was not the only

published trial that was reviewed by the appraisal committee; other smaller cross-over studies were also reviewed, although DANPACE was the largest trial.

The Committee considered the clinical evidence for dual-chamber pacemakers compared with single-chamber atrial pacemakers for those with symptomatic bradycardia due to sick sinus syndrome without atrioventricular block. There were no statistically significant differences shown for the whole population for several important outcomes, including mortality, stroke, quality of life and heart failure. However, dual-chamber pacemakers were associated with a statistically significant reduction in (1) paroxysmal atrial fibrillation; (2) the need to change pacing mode and (3) the need for re-operation. Clinical experts consulted accepted that there was no difference in terms of clinical outcomes such as mortality, but there was a reduced need for re-operation with a dual chamber pacemaker.

PACEF Recommendation:
PACEF has been advised that this Technology Appraisal is accepted as best practice and has already been implemented within ULH Cardiology.

NICE TECHNOLOGY APPRAISAL 325: *NALMEFENE FOR REDUCING ALCOHOL CONSUMPTION IN PEOPLE WITH ALCOHOL DEPENDENCE* (NOVEMBER 2014)

Nalmefene is recommended within its marketing authorisation, as an option for reducing alcohol consumption, for people with alcohol dependence:

- who have a high drinking risk level (i.e. they are still drinking more than 7.5 units per day (men) or more than 5 units per day (women) 2 weeks after an initial assessment).
- who do not have physical withdrawal symptoms.
- who do not need to stop drinking straight away or completely (i.e. immediate detoxification).

The marketing authorisation states that nalmefene should only be prescribed in conjunction with psychosocial support focused on treatment adherence and reducing alcohol consumption. It should only be initiated in patients who continue to have a high drinking risk level 2 weeks after initial assessment.

Notes

In January 2014, PACEF considered a New Drug Assessment of nalmefene tablets 18mg (*Selincro*). While PACEF were interested in the product and considered that it may have a role in helping high-risk drinkers to reduce their alcohol consumption, concerns were raised around:

(1) The level of support required to evaluate patients and support them through therapy.
(2) The place of nalmefene within the wider context of commissioned alcohol services and the role of these services in the provision of nalmefene or the support of patients taking nalmefene.
(3) The need for objective outcome measures and assurances that the treatment is proving to be effective.

Ultimately, nalmefene 18mg tablets (*Selincro*) were approved for inclusion in the *Lincolnshire Joint Formulary*, but for the restricted use of specialist services only; designation: RED.

Following review of the NICE TA, PACEF remain reluctant to approve nalmefene for wider GP prescribing for a number of reasons:

(1) Need for psychosocial support

There are three randomized controlled trials in adults with alcohol dependence comparing 18mg nalmefene on an as-needed basis plus psychosocial support with placebo plus psychosocial support. These are ESENSE1 (n=604), ESENSE2 (n=718) and SENSE (n = 675). ESENSE1 and ESENSE2 were identical efficacy studies with a follow up of 24 weeks; SENSE was primarily designed to collect safety data up to 12 months, although after the study had started the protocol was amended to include efficacy analysis.

All three studies used BRENDA as the form of psychosocial support focusing on treatment adherence and reduction in alcohol consumption. BRENDA has 6 components: (i) a Biopsychosocial evaluation; (ii) a Report of findings from the evaluation given to the patient; (iii) Empathy; (iv) addressing patient Needs; (v) providing Direct advice and (vi) Assessing patient reaction to advice and Adjusting the treatment plan as needed. All sessions were provided by trained professionals and were delivered at weekly intervals for the first 2 weeks and then monthly. Sessions lasted for 15-30 minutes except for the first longer session of 30-40 minutes.

PACEF Comment:
The level of psychosocial support provided in the trials is significantly beyond existing primary care capacity. Nalmefene is likely to be less effective without the optimum level of support provided in trials. Both the NICE Evidence Review Group and the manufacturer state that brief intervention would be sufficient for most patients.

(2) Exclusion of patients with severe medical co-morbidities and severe psychiatric co-morbidities from trials

To be included in the studies patients must have had 14 or fewer days of abstinence in the 28 days preceeding the screening visit. They must have been at medium drinking risk level or higher (i.e. more than 5 units per day in men and 2.5 units per day in women). People with severe medical co-morbidities were excluded from all three RCTs; people with severe psychiatric co-morbidities were excluded from ESENSE1 and 2.

PACEF Comment:
The current marketing authorisation for *Selincro* was granted on the basis of a post hoc analysis in a subgroup of patients in all three studies that were at high or very high drinking risk level. The NICE Evidence Review Group were concerned that patients with severe medical and psychiatric co-morbidities were excluded from the RCTs as this made the safety and efficacy of nalmefene in these patient groups uncertain.

(3) Patient self-reporting of outcomes in trials

The primary outcomes in ESENSE1 and 2 were changes from baseline in number of heavy drinking days per month and total alcohol consumption at month 6. Patients self-reported their daily alcohol consumption. The primary outcomes in SENSE were changes from baseline in number of heavy drinking days per month and total alcohol consumption at month 6. Again, patients self-reported their daily alcohol consumption.

PACEF Comment:
Self-reporting of alcohol intake and progress could have significantly distorted or biased the results of these studies. GPs prescribing nalmefene would be entirely

dependent upon patient or carer testimony to determine progress and outcomes. It would be extremely easy for a GP to be drawn into poorly controlled ongoing prescribing of nalmefene with very little objective evidence of benefit or improvement.

(4) Clinical evidence

The post hoc analysis in those at high or very high DRL showed greater reductions in number of heavy drinking days and total alcohol consumption in patients treated with nalmefene plus BRENDA compared to placebo plus BRENDA. The NICE Evidence Review Group concluded that nalmefene plus BRENDA reduces the number of heavy drinking days and total alcohol consumption compared to BRENDA alone, although the exact magnitude of the effect was uncertain due to the post hoc subgroup analysis not being sufficiently powered.

PACEF Comment
PACEF accepted this evidence of efficacy as part of our last evaluation of the product. The NICE Evidence Review Group has expressed some concern over the reliability of the results of the post hoc analysis as the three studies were not sufficiently powered for this. They also raise high dropout rates as a concern; 13% in the active treatment group compared to 6% in the placebo group. High dropout rates in practice could result in increasing prescribing costs with little objective evidence of patient benefit unless closely monitored and supported.

PACEF Recommendation
Trial evidence suggests that the potential benefits of nalmefene in patients with a high drinking risk level are dependent upon initial evaluation using a two week alcohol consumption diary to identify appropriate patients followed by continuous psychosocial support focused on treatment adherence and reduction of alcohol consumption for those that end up on prescribed therapy. As this level of support is only available through specialist alcohol services, nalmefene tablets 18mg (*Selincro*) are only approved for restricted use within the *Lincolnshire Joint Formulary* and are designated RED. Primary care clinicians are encouraged to undertake opportunistic screening for alcohol use disorders using the Alcohol Use Disorders Identification Test (AUDIT); referral to specialist services is recommended for all patients scoring 20-40.

NICE TECHNOLOGY APPRAISAL 326: *IMATINIB FOR THE ADJUVANT TREATMENT OF GASTROINTESTINAL STROMAL TUMOURS* (NOVEMBER 2014)

Imatinib is recommended as an option as adjuvant treatment for up to 3 years for adults who are at high risk of relapse after surgery for KIT (CD117)-positive gastrointestinal stromal tumours, as defined by the Miettinen 2006 criteria (based on tumour size, location and mitotic rate).

PACEF Recommendation:
Imatinib tablets 100mg and 400mg (*Glivec*) are approved for use for a maximum treatment period of 3 years as an adjuvant treatment for adults who are at high risk of relapse after surgery for KIT (CD117)-positive gastrointestinal stromal tumours. They are included in the *Lincolnshire Joint Formulary* for this indication; designation RED.

NHS ENGLAND PATIENT SAFETY ALERT: *RISK OF DEATH OR SERIOUS HARM FROM ACCIDENTAL INGESTION OF POTASSIUM PERMANGANATE PREPARATIONS* (DECEMBER 2014)

Potassium permanganate is used in wound care for its antiseptic and antimicrobial properties. It is available as a solution for further dilution and as a tablet that can be dissolved in water and diluted to a specified concentration. Potassium permanganate in any formulation is for external use only and can be fatal if ingested orally due to local inflammatory reactions that block the airways or cause perforation of the gastro-intestinal tract. It can also cause death through toxicity and organ failure. The National Reporting and Learning System (NRLS) has identified 43 incidents in the last three and a half years where potassium permanganate tablets have been ingested orally by patients. In one incident reported in Lincolnshire, a non-English speaking patient misunderstood instructions for use.

PACEF Recommendations:

As the risk of error seems to increase when the term potassium permanganate tablets is used, consideration should be given to using the term potassium permanganate soak on dispensed labels and in patient notes. Care should be taken to ensure that the patient is fully aware of how to use potassium permanganate tablets and realises that the product is for external use only. Particular care should be taken when prescribing and dispensing potassium permanganate tablets to vulnerable patients in their own homes. If accidental ingestion occurs, it must be treated as a medical emergency.

NHS ENGLAND PATIENT SAFETY ALERT: *RISK OF DEATH AND SERIOUS HARM FROM DELAYS IN RECOGNISING AND TREATING INGESTION OF BUTTON BATTERIES* (DECEMBER 2014)

The ingestion of button batteries can cause serious harm and death. Severe tissue damage results from a build-up of sodium hydroxide as a result of the electrical current discharged from the battery. Sodium hydroxide causes tissue burns, often oesophageal, which can cause fistulisation into major blood vessels, resulting in catastrophic haemorrhage. **If accidental ingestion of a button battery occurs, it must be treated as a medical emergency.**

Acknowledgements

Many thanks to: Cathy Johnson, Interface Lead Pharmacist , Robyn Thompson, Senior Pharmacist, United Lincolnshire Hospitals Trust and Shiraz Haider, Chief Pharmacist, Lincolnshire Partnership Foundation Trust for their help with the compilation of this *Bulletin*.

Stephen Gibson
Head of Prescribing and Medicines Optimisation
Greater East Midlands Commissioning Support Unit

February 2014