NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 5; Number 18 **December 2011**

What's new this month?

- **Following an MHRA re-evaluation of the risks and benefits of reboxetine (Edronax), this drug has had its designation changed from RED-RED to AMBER without shared-care (see page 3).**
- **Exenatide prolonged release injection (Bydureon) is approved for use as an alternative to twice daily exenatide (Byetta) where the twice daily product is poorly tolerated (see page 3).**
- **Citalopram has been associated with dose dependent QT interval prolongation. Advice is given on reviewing patients, appropriate action and potential alternatives (see page 6).**
- **Further safety concerns relating to dronedarone (Multaq) have resulted in additional restrictions to use (see page 8).**
- **New guidance is given on the use of Seretide 250 metered dose inhaler in patients with chronic obstructive pulmonary disease (see page 10).**
- **New shared care guidelines are available covering ketamine for use in palliative care and chronic neuropathic pain (see page 9).**
- **Updated advice on supply problems with insulin glulisine (Apidra) is provided (see page 12).**

CONTENTS

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

SUMMARY OF PACEF DECISIONS: OCTOBER 2011 UPDATE

Drug	Indication(s)	Traffic Light Status
Bivalirudin injection (Angiox)	Licensed for use in combination with aspirin and clopidogrel for the treatment of adults with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI).	RED
Citalopram tablets 10mg/20mg/40mg	Licensed for depressive illness and panic disorder	GREEN Subject to new dosage recommendations. No longer recommended first line.
Dronedarone tablets 400mg (Multaq)	Licensed for use in clinically stable patients with previous or current non-permanent atrial fibrillation	AMBER Shared care guideline required.
Exenatide prolonged release injection (Bydureon)	Licensed for use as dual therapy with metformin, a sulfonylurea or a glitazone or as triple therapy with metformin plus a sulfonylurea or metformin plus a glitazone in type 2 diabetes inadequately controlled on maximally tolerated doses of these oral therapies	GREEN As an alternative exenatide formulation in patients experiencing intolerance to twice daily exenatide.
Ketamine injection (Ketalar)	Unlicensed indication. For use either orally or subcutaneously in palliative care or chronic neuropathic pain for the management of pain unresponsive to standard therapies	AMBER Shared Care Guideline now available
Ketamine oral solution 50mg in 5ml	Unlicensed. For use in palliative care or chronic neuropathic pain for the management of pain unresponsive to standard therapies.	AMBER Shared Care Guideline now available
Reboxetine tablets 4mg (Edronax)	Licensed for the treatment of major depression	AMBER NB For severe clinical depression only; no shared care guideline is required.
Sodium valproate modified release granules 50mg, 100mg, 250mg. 500mg, 750mg, 1000mg (Epilim Chronospheres)	Licensed for all forms of epilepsy	GREEN For paediatric use only

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care.**

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

NEW DRUG ASSESSMENTS

REVIEW: *REBOXETINE (EDRONAX)*

In the February 2011 issue of the *PACE Bulletin* (Vol 5 No 3), we published the results of a PACEF review of the findings of a recently published and highly publicised German health technology assessment of reboxetine (Edronax)[1]. This systematic review and meta-analysis of 13 double-blind RCTs (4098 adults) compared reboxetine to placebo or an SSRI in the management of depression[2]. The authors concluded, after a review of published and unpublished data, that reboxetine showed no benefit over placebo and was inferior to SSRIs in terms of remission and 50% response rates. Using only published data, reboxetine was reported to be more effective than placebo and similar in efficacy to SSRIs. This was claimed to reveal evidence of publication bias which significantly overestimated the benefit of reboxetine and underestimated the harm. In response to this, PACEF changed the designation of reboxetine (Edronax) from AMBER to RED-RED.

Most recently, the Medicines and Healthcare products Regulatory Agency (MHRA) has published its own assessment of the risks and benefits of reboxetine and has concluded that the German analysis omitted certain studies involving reboxetine from its efficacy evaluation[3]. Taking these studies into account the MHRA and the European Pharmacovigilance Working Party have concluded that **there is evidence to support a statistically significant benefit of reboxetine over placebo in patients with severe clinical depression.** No such evidence of benefit was found in mild to moderate depression.

PACEF Recommendation:
In view of the MHRA assessment, PACEF now acknowledge a role for reboxetine (Edronax) in severe clinical depression. As a result of this, reboxetine is re-designated AMBER without the need for a shared care guideline. Reboxetine must be initiated by a specialist in mental health, but can be prescribed by a GP following specialist recommendation or initiation. There is no role for reboxetine in the treatment of mild to moderate depression.

References
1. *PACE Bulletin* Vol 5 No 3 (February 2011)
2. Eyding D et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *BMJ* 2010;341:c4737
3. MHRA UK Public Assessment Report, *Reboxetine: a review of the benefits and risks* (September 2011).

NEW FORMULATION ASSESSMENT: *EXENATIDE 2MG PROLONGED RELEASE INJECTION (BYDUREON)*

Exenatide is a glucagon like peptide -1 (GLP-1) receptor agonist licensed for the management of type 2 diabetes in adult patients failing to achieve adequate glycaemic control on maximally tolerated doses of oral therapies. Exenatide 2mg prolonged release injection (Bydureon) is a once weekly formulation of exenatide launched as an alternative to the original twice daily injection Byetta. In Bydureon, the exenatide has been incorporated into polymer-based (Medisorb) microspheres. Following subcutaneous injection, these microspheres slowly biodegrade to release exenatide gradually at a controlled rate. There is also some “free exenatide” not absorbed into the polymer which provides an instant effect before the polymer spheres degrade. Bydureon is licensed for use as dual therapy with metformin, a sulfonylurea or a glitazone or as triple therapy with metformin plus a sulfonylurea or

metformin plus a glitazone in type 2 diabetes inadequately controlled on maximally tolerated doses of these oral therapies.

PACEF last issued guidance on exenatide (Byetta) in August 2009 (*PACE Bulletin* Vol 3 No 9) as follows:

PACEF Recommendation:
Exenatide (Byetta) is classified as GREEN. Treatment should primarily be initiated by a diabetologist or a GP with a Special Interest in diabetes (GPSI), although the GREEN status allows for broader GP initiation. Exenatide initiation should only be considered at Step Three of the NICE Clinical Guideline for the management of type 2 diabetes mellitus.

Clinical evidence to support the use of exenatide prolonged release (Bydureon) comes from a series of phase 3 studies known as the DURATION trials which compared prolonged release exenatide to a range of established alternative treatments including twice daily exenatide, sitagliptin, insulin glargine, pioglitazone and liraglutide 1.8mg. Results from these clinical trials demonstrate that the once weekly formulation offers continuous glycaemic control over a 7 day period resulting in mean reductions of HbA1c between 1.3 and 1.9. There are still no studies involving any formulation of exenatide that demonstrate improved outcomes such as reduced risk of macrovascular or microvascular events.

The most common adverse effects associated with exenatide therapy are nausea, vomiting, diarrhoea and constipation. From trials, the incidence of adverse effects is lower with the weekly formulation than with the twice daily product. It is thought that this decrease in adverse events could be related to the pharmacokinetic properties of the prolonged release formulation which do not create the high post dose plasma levels associated with twice daily exenatide.

Exenatide (Byduroen) requires reconstitution before it can be administered. Although clear instructions are provided, patients and or their carers will require some degree of training in order to ensure they are able to prepare and administer the injection correctly.

A cost comparison with standard twice daily exenatide and liraglutide reveals the following:

Drug	**Dose range**	**Cost (£) (30 days)**
Exenatide 2 mg	2mg weekly	£73.26 (28 days)
Exenatide 10mcg	10mcg twice daily	£68.24
Liraglutide 1.2mg	Once daily	£78.48

PACEF Recommendation:
PACEF are satisfied that exenatide prolonged release injection (Bydureon) provides continuous glycaemic control over a seven day period comparable to alternatives. It offers the advantage of once weekly injection and does not require initial dosage titration in contrast to alternative GLP-1 receptor agonists. It also seems to be better tolerated than the original twice daily exenatide formulation. However, assembly and administration of the injection may be a challenge for some patients and the product is more expensive than the twice daily formulation. Exenatide prolonged release injection (Bydureon) is designated GREEN. Treatment should primarily be initiated by a diabetologist or a GP with a Special Interest in diabetes (GPSI), although the GREEN status allows for broader GP initiation. It should be considered as an option for patients who are indicated for exenatide treatment, but who cannot tolerate the twice daily formulation. Once weekly exenatide should be considered in preference to liraglutide.

NICE advice in relation to exenatide:
Consider adding a GLP-1 mimetic (exenatide) as third line therapy to first line metformin and a second line sulfonylurea when control of blood glucose remains or becomes inadequate (HbA1c > 7.5% or other higher level agreed with the individual) and the person has:
(1) a BMI >35kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological, biochemical or physical problems arising from high body weight or
(2) a BMI < 35kg/m^2 and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities.
Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months).

Prescribers are also reminded of the well documented risk of pancreatitis with exenatide. MHRA advice to healthcare professionals is as follows:

- **There have been reports of necrotising and haemorrhagic pancreatitis with exenatide, some of which were fatal.**
- **If pancreatitis is suspected, treatment with exenatide should be suspended immediately; if pancreatitis is diagnosed, exenatide should be permanently discontinued.**
- **Diagnosed pancreatitis with an unexpectedly prolonged course, haemodynamic instability, fever, failure of medical therapy, or presence of fluid collections on CT suggests possible necrosis.**
- **Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30ml/min)**

RAPID DRUG ASSESSMENT: *MODIFIED RELEASE SODIUM VALPROATE GRANULES (EPILIM CHRONOSPHERES)*

Modified release (MR) sodium valproate granules (Epilim Chronospheres) are licensed for all forms of epilepsy. They can be swallowed whole with a cold drink or sprinkled onto cold soft food and swallowed without chewing and can be useful both for children and for adult patients with swallowing difficulties. Since the original PACEF assessment of this formulation in January 2009, many additional strengths of the product have been launched providing a much wider range of dosage options than the competing product Episenta granules. A cost comparison of the two products reveals that despite the fact that Episenta is considerably less costly at both the 500mg and 1000mg dose, it offers only a fraction of the strengths available in the Epilim Chronospheres range.

Drug	Strength	Cost (£)
		30 sachets
Epilim Chronospheres	50mg	£30.00
	100mg	£30.00
	250mg	£30.00
	500mg	£30.00
	750mg	£30.00
	1000mg	£30.00
		100 sachets
Episenta granules	500mg	£18.00
	1000mg	£35.50

PACEF Recommendation:
Both of the MR sodium valproate granule formulations (Epilim Chronospheres and Episenta Granules) are designated GREEN. Episenta Granules are lower in price than Epilim Chronospheres, but are only available in 500mg and 1000mg strengths; where other doses are required Epilim Chronospheres will need to be prescribed.

DRUG SAFETY UPDATE

CITALOPRAM ASSOCIATED WITH DOSE-DEPENDENT QT INTERVAL PROLONGATION

A recent, so-far unpublished study has assessed the effects of 20mg and 60mg citalopram on the QT interval in healthy adults. Compared to placebo, the mean change from baseline in QTcF (Fridericia correction) was 7.5 msec for the 20mg daily dose and 16.7msec for 60mg daily. The conclusion is that citalopram is associated with dose-dependent QT interval prolongation. Increasing QTc interval prolongation is progressively associated with increased risk of Torsade de Pointes (TdP), an atypical ventricular tachyarrhythmia which itself can progress to ventricular fibrillation. This finding correlates with cases of ventricular arrhythmia reported during the post-marketing period of citalopram which occurred predominantly in female patients with hypokalaemia and pre-existing QT interval prolongation or in those with other cardiac diseases.

In response to this new evidence, Lundbeck have announced a series of changes to the Summary of Product Characteristics for Cipramil as follows:

- The recommended maximum dose in adults has been reduced from 60mg to 40mg daily. Similarly the recommended maximum dose in the elderly has

dropped from 40mg to 20mg. In patients with reduced hepatic function the recommended maximum dose has been reduced from 30mg to 20mg.

- Contra-indications have been expanded to include known QT interval prolongation or congenital long QT syndrome. Co-administration with other drugs known to prolong the QT interval is also contra-indicated.
- Caution is advised in patients at higher risk of developing TdP (e.g. those with congestive heart failure, recent MI, bradyarrhythmias or a predisposition to hypokalaemia or hypomagnesaemia because of concomitant illness or medicines).

So far, the American Food and Drug Administration (FDA) have reviewed the results of this study and issued advice to American healthcare professionals. The Medicines and Healthcare Products Regulatory Agency (MHRA) has yet to issue advice to healthcare professionals in the UK.

PACEF Recommendations:

Prescribers are advised to review at the next appointment all patients currently taking citalopram for any indication:

(1) to ensure that those above the new recommended maximum doses are identified with a view to gradual dose reduction to within the revised range;

(2) to ensure that all those with identified contra-indications are moved to an alternative therapy;

(3) to ensure that all those now associated with cautions or potential interactions are identified and considered for possible change of therapy dependent on an assessment of risks and benefits.

Existing patients should be enabled to continue with citalopram therapy where they and their clinician consider it to be appropriate to do so. Where necessary dose reductions result in reduced treatment effectiveness or relapse, consideration will need to be given to alternative therapy. All new initiations of citalopram should be within the new SPC defined doses, cautions and contra-indications. Within the context of the NICE Clinical Guideline on the treatment of depression, alternative first line options are fluoxetine and sertraline, with sertraline emerging as the drug of choice post-MI and in heart failure. Patients taking citalopram should be advised to contact a healthcare professional immediately if they experience signs and symptoms of abnormal heart rate or rhythm. Patients should not stop taking citalopram or reduce their dose without support from a healthcare professional as withdrawal symptoms can occur, particularly following abrupt withdrawal.

A local review of published case reports, clinical papers and Committee on Safety of Medicines (CSM) reports has revealed that QT interval prolongation and TdP have been seen with all SSRIs and could be a class effect. However, the small number of reports suggests that this problem rarely becomes symptomatic and then usually only in overdose. Tricyclic antidepressants are also known to exhibit this effect and are thought to be more commonly associated with QT interval prolongation than SSRIs. As a result of this, citalopram continues to be designated GREEN and can continue to be prescribed subject to the constraints defined by the more restrictive SPC. Switching existing citalopram patients to escitalopram (the S-enantiomer of citalopram) is not recommended as cases of QT interval prolongation have also been reported with this drug (and other SSRIs). Further guidance in relation to citalopram safety concerns and alternative therapies is in preparation in conjunction with Lincolnshire Partnership Foundation Trust. There is an ongoing review led by the regulatory authorities into safety

concerns around citalopram and the wider implications for the use of all SSRIs. Further guidance is likely to be issued by the MHRA in due course.

References:
Lundbeck Ltd, *Association of Cipramil (citalopram hydrobromide) with dose-dependent QT interval prolongation* (24th October 2011)
Food and Drug Administration Drug Safety Communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide) (August 2011)

EUROPEAN MEDICINES AGENCY GUIDANCE RECOMMENDS RESTRICTING THE USE OF DRONEDARONE (MULTAQ)

In *PACE Bulletin* Vol 5 No 12 (July 2011), we reported on an ongoing risk-benefit analysis of dronedarone which was being undertaken by the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP). This review has now been completed and has concluded the following:

- Treatment with dronedarone should be restricted to the maintenance of sinus rhythm after successful cardioversion in patients with paroxysmal or persistent atrial fibrillation (AF). It is no longer indicated for use in patients when AF is still present.
- Dronedarone must not be used in patients with permanent AF, heart failure or left ventricular systolic dysfunction.
- Treatment with dronedarone should only be started and monitored by a specialist.
- In view of the increased risk of liver, lung and cardiovascular events, dronedarone should only be prescribed after alternative treatment options have been considered.
- Dronedarone must not be used in patients who have had previous liver or lung injury following treatment with amiodarone.
- Patients on dronedarone should have their lung and liver function as well as their heart rhythm regularly monitored. Liver function should be closely monitored during the first few weeks of treatment.
- Doctors should consider discontinuation of treatment if AF reoccurs
- Patients currently taking dronedarone should have their treatment reviewed at their next appointment.
- Dronedarone is now contra-indicated in patients with: (1) unstable haemodynamic conditions; (2) history of, or current, HF or left ventricular systolic dysfunction; (3) permanent AF (i.e. duration $\geq$ 6 months or unknown and attempts to restore sinus rhythm no longer considered by a physician); (4) liver and lung toxicity related to previous use of amiodarone.

PACEF Recommendation:
Existing shared care guidelines for dronedarone in the treatment of patients with non-permanent AF have been reviewed with a revised version due for ratification by PACEF in November. Within the context of licensed indications (i.e. non-permanent AF), dronedarone (Multaq) remains AMBER and subject to shared care guidelines. The Medicines and Healthcare products Regulatory Agency (MHRA) have already warned of the risk of cardiac failure and hepatotoxicity associated with dronedarone which was highlighted to all prescribers in *PACE Bulletin* Vol 5, No 5 (March 2011). Existing patients should be advised to remain vigilant for the symptoms of heart failure (HF) or worsening of existing symptoms (e.g. weight gain, dependent oedema, increased dyspnoea). If HF develops or worsens, consider suspending or discontinuing dronedarone. Patients should also be advised to remain vigilant

for the symptoms of liver injury (e.g. abdominal pain or discomfort, loss of appetite, nausea, vomiting, yellowing of the skin or whites of the eye, darkening of the urine, itching or fatigue). The revised SCG will also provide more guidance on monitoring for symptoms of lung fibrosis. All patients currently receiving dronedarone should have liver function tests performed before treatment, on a monthly basis for 6 months, at months 9 and 12 and periodically thereafter. This and other monitoring requirements are detailed in the existing SCG and will be expanded upon in the revised version due for ratification by PACEF in November 2011.

References:
European Medicines Agency, Press Release: EMA recommends restricting use of Multaq (22 September 2011)
MHRA, *Drug Safety Update*, Dronedarone (Multaq): cardiovascular, hepatic and pulmonary adverse events – new restrictions and monitoring requirements, Vol 5 No 3 (October 2011)

NEW EAST MIDLANDS GUIDANCE ON THE USE OF LABA/ICS COMBINATION INHALERS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

In *PACE Bulletin* Volume 5 No 1 (January 2011), we detailed the NICE Clinical Guideline on the management of Chronic Obstructive Pulmonary Disease (COPD). NICE have recommended that **for people requiring regular maintenance inhaled therapy with an FEV1 less than 50% predicted and frequent exacerbations either a Long Acting Beta Agonist (LABA)/inhaled corticosteroid (ICS) combination inhaler or a Long Acting Muscarinic Antagonist (LAMA) should be prescribed.**

Existing PACEF advice is as follows:

Where a LABA/ICS combination inhaler is indicated, only licensed products at licensed doses for COPD should be prescribed (i.e. Symbicort 400/12 (1 puff twice daily) or Seretide 500 Accuhaler (1 puff twice daily). Prescribers are reminded that LABA/ICS combination inhalers used in the treatment of COPD need to be prescribed at doses licensed for COPD. The two licensed products are comparably priced with Symbicort Turbohaler marginally lower in cost than Seretide 500 Accuhaler. Seretide 250 metered dose inhaler is not licensed for use in COPD and should not be prescribed for this indication.

More recent advice issued by Dr Mike Ward (Clinical Lead COPD, NHS East Midlands) on behalf of the NHS East Midlands Respiratory Network has recognised that, despite its unlicensed status and high cost, the Seretide 250 metered dose inhaler (MDI) continues to be widely prescribed for COPD. Updated advice from the Network reads as follows:

LABA/ICS combination inhalers do not have a licence in COPD. Licensed dry powder inhalers (DPI) are preferred. However, where an MDI is preferred, prescribers are advised to use a Seretide 125 MDI (£35.00) with a large volume spacer device rather than the 250 MDI (£59.48). The lung deposition of drug is enhanced by using the large volume spacer. There are no studies using MDI combinations in COPD; we await further evidence.

PACEF have reviewed the evidence behind this recommendation. It derives from a single trial published in *Chest* in 1999 which demonstrated that the use of a large volume spacer with a fluticasone MDI doubled the dose of fluticasone delivered to the lungs compared to a fluticasone MDI used alone[1]. The Respiratory Network have extrapolated from this to conclude that the Seretide 125 inhaler (MDI) plus a large

volume spacer at 2 puffs twice daily is equivalent to Seretide Accuhaler 500mcg 1 puff twice daily. Following careful consideration of this advice and the evidence base behind it, PACEF have amended their existing advice as follows:

PACEF Recommendation: LABA/ICS Combination Inhalers in COPD

Seretide 125 and 250 MDIs are not licensed for use in COPD and should not routinely be prescribed for this indication. However, where use of an MDI is preferred or unavoidable and a LABA/ICS combination inhaler is indicated, the Seretide 125 MDI plus a large volume spacer should be prescribed in preference to the Seretide 250 MDI. All patients currently prescribed the Seretide 250 MDI for COPD should be identified and reviewed with a view to changing therapy to a licensed preparation (see above) or a Seretide 125 MDI plus a large volume spacer. Patients established on Seretide 250 MDI plus a large volume spacer may be particularly challenging to review due to severity of disease, difficulties in diagnosis, co-morbidities and multiple concurrent medication. For such individuals, it may be appropriate to seek specialist advice. For some patients, even after thorough review, continuation on Seretide 250 MDI plus a large volume spacer may remain appropriate.

Reference:

1. Owen J et al, 'Evaluation of the effect of a large volume spacer in the systematic bioactivity of fluticasone propionate metered dose inhaler', *Chest* 1999; 116; 935-940

SHARED CARE GUIDELINES: *KETAMINE FOR USE IN PALLIATIVE CARE AND CHRONIC NEUROPATHIC PAIN*

As reported in *PACE Bulletin* Volume 5 No 15 (September 2011), ketamine oral solution (50mg in 5ml) and injection have been approved for use in palliative care for the management of pain unresponsive to standard therapies. PACEF designated these products as AMBER subject to the development of shared care guidelines. These guidelines have now been developed and, following detailed discussion with the ULH Pain Service, have been extended to incorporate chronic neuropathic pain. The SCG is entitled:

> *Ketamine for use in palliative care for the management of pain unresponsive to standard therapies and as a third/fourth-line choice for the management of chronic neuropathic pain that has failed to respond to alternative treatments* (October 2011)

Copies should be issued by palliative care and ULH Pain Service consultants in conjunction with every request for a GP to participate in shared care with ketamine. The full text SCG is available on the NHS Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF. Copies are also available on request from Cathy Johnson, the Interface Lead Pharmacist (cathy.johnson@lpct.nhs.uk).

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 230: *BIVALIRUDIN FOR THE TREATMENT OF ST-SEGMENT-ELEVATION MYOCARDIAL INFARCTION* (JULY 2011)

Key Recommendation:

Bivalirudin in combination with aspirin and clopidogrel is recommended for the treatment of adults with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI).

PACEF Recommendation:
Bivalirudin injection (Angiox) is licensed for use in combination with aspirin and clopidogrel in acute coronary syndromes in patients planned for urgent or early intervention and for anti-coagulation for patients undergoing (PCI). It is designated RED for use in combination with aspirin and clopidogrel for the treatment of adults with ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI).

NEW TRIALS IN BRIEF

Increasing use of insulin analogues across the NHS

This study aimed to characterise the pattern of insulin prescriptions dispensed in the UK between 2000 and 2009 and to evaluate the financial impact on the NHS of increased use of analogue insulins as an alternative to human insulins in comparable devices. Adjusting the costs for inflation and using 2010 prices, over the 10 year period of the study:

- The total annual cost of insulins increased from £156M to £359M (up 130%).
- The annual cost of analogues increased from £18.2M to £305M.
- The annual cost of human insulin decreased from £131M to £51M.
- Assuming that half of all patients using analogues could have received human insulin the overall incremental cost of analogue insulin was £312M (£66M in 2009).

PACEF Comment: In the first quarter of 2011/12, the cost of insulin analogues in Lincolnshire was £783K from a total spend on insulins of almost £1.1M. The NHS Prescription Pricing Division report that over the same period in Lincolnshire 90.5% of all intermediate and long acting insulins were prescribed as analogues compared to Strategic Health Authority (SHA) and England averages of 78% and 85% respectively. The National Prescribing Centre has highlighted this as an area that NHS organisations should scrutinise as part of their QIPP plans. NICE guidance on the management of type 2 diabetes recommends that human NPH insulin should be the insulin preparations of choice. Long acting insulin analogues can be considered for those who fall into specific categories (e.g. those who require assistance to administer insulin or those with problematic hypoglycaemia). NICE found that the cost effectiveness of long-acting insulin analogues was not favourable with an incremental cost per QALY greater than £100,000 in all scenarios; similar conclusions have been reached by the Canadian Agency for Drugs and Technologies in Health and the Institute for Quality and Efficiency in Healthcare (IQWiG) in Germany. The *Drug and Therapeutics Bulletin* reviewed insulin use in type 2 diabetes in December 2010 and concluded that for most people analogue insulins offer no significant clinical advantage and are much more expensive. Despite this, prescribing trends across the NHS and in

Lincolnshire have been shifting alarmingly towards massively increased use of insulin analogues. PACEF will be undertaking further work in relation to this issue in the coming months.

Reference:
Holden SE et al. Evaluation of the incremental cost to the National Health Service of prescribing analogue insulin. *BMJ Open* 2011; 2:e000258

UPDATED ADVICE ON SUPPLY PROBLEMS WITH INSULIN GLULISINE (APIDRA)

Sanofi- Aventis are informing all healthcare professionals that interruptions in the supply of insulin glulisine (Apidra) are now likely to last until March 2012. Supplies are still being maintained for those classed as vulnerable patients (i.e. those under 18 years, over 70 years , pregnant patients or those classed as having brittle diabetes who have failed to respond to previous treatment with rapid acting insulin) but others will need to be switched to alternative rapid acting insulins.
Suitable alternative products might be insulin aspart (NovoRapid) or insulin lispro (Humalog). Further advice on appropriate alternative products and doses can be obtained from the Sanofi-Aventis Medical Information Service or the Lincolnshire Community Diabetes team. If switching to alternative insulin, it is usual to reduce the current dose by 10-20% and titrate according to response. However, this will vary according to individual patient circumstances and all prescribers are advised to seek advice if they are not experienced in changing insulin therapy. Supplies of Apidra insulin vials remain unaffected and this might present a suitable alternative for some patients. Full details on the supply problems around insulin glulisine can be found in *PACE Bulletin* Vol 5 No 16 (October 2011).

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