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

Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 11 **July 2013**

What's new this month?

- **Eplerenone (*Inspra*) is approved for use in left ventricular dysfunction (LVEF ≤ 30%) and heart failure (NYHA II). Designation GREEN (see page 3).**
- **Nepafenac 1mg/ml eye drops (*Nevanac*) have not been approved for the reduction in risk of post-operative macular oedema associated with cataract surgery in diabetic patients. Designation: RED-RED. Ketorolac 0.5% eye drops (*Acular*) remain the preferred ocular NSAID. Designation: AMBER (see page 4).**
- **Racecadotril sachets 10mg/30mg (*Hidrasec Infant*/*Hidrasec Children*) and capsules 100mg (*Hidrasec*) have not been approved for the treatment of acute diarrhoea and are designated RED-RED (see page 4).**
- **Lisdexamfetamine capsules (*Elvanse*) are approved for use in the treatment of Attention Deficit Hyperactivity Disorder in children ≥ 6 years when response to methylphenidate is considered inadequate. Designation: AMBER (see page 5).**
- **Lixisenatide 10microgram/20microgram injection (*Lyxumia*) is designated GREEN subject to NICE criteria for the treatment of type 2 diabetes mellitus. Lack of comparative data against other GLP-1 mimetic agents and lack of long-term safety data mean that PACEF have been unable to endorse the product as the first line GLP-1 mimetic agent of choice despite its lower cost (see page 7).**
- **All remaining patients taking cilostazol 50mg and 100mg tablets (*Pletal*) to improve their walking distance with intermittent claudication should be reviewed in accordance with new contraindications. Following an MHRA safety review, contraindications now include unstable angina, recent myocardial infarction or coronary intervention (within 6 months), history of severe tachyarrhythmia and concurrent prescribing of two or more antiplatelet or anticoagulant agents. There should be no new initiations of cilostazol (*Pletal*) as it has been designated RED-RED (see page 9).**
- **As a result of emerging safety concerns, strontium ranelate granules (*Protelos*) are no longer considered appropriate for GP initiation and have been reclassified as AMBER with shared care. New patients should only be initiated on strontium ranelate on the advice of a specialist with experience in the treatment of osteoporosis and within the context of a shared care guideline that is currently in development. Existing patients should be reviewed in accordance with MHRA guidance at their next routine appointment and consideration given to stopping therapy where a contra-indication is identified or where the risk of ongoing therapy is thought to outweigh the potential benefits (see page 10).**
- **The *Flutter* oscillating positive expiratory pressure (PEP) device was approved for use by PACEF in February 2013 for patients with mucus producing conditions who are insufficiently responsive to active cycle of breathing techniques (ACBT). It should only be prescribed following patient assessment and recommendation of a PEP device by a specialist respiratory physiotherapist. Designation: AMBER. Specialist physiotherapists have now produced a treatment algorithm to clearly identify when prescriptions for the product are likely to be requested from GPs (see page 11).**

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SUMMARY OF PACEF DECISIONS: *MAY 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Colistimethate sodium DPI (*Colobreathe*)	For the management of chronic pulmonary infections caused by *P.aeruginosa* in patients with cystic fibrosis (CF) aged 6 years and older.	AMBER subject to shared care Approved for inclusion on the Joint Formulary
Cilostazol 50mg and 100mg tablets (*Pletal*)	For the improvement of walking distances in patients with intermittent claudication who do not have rest pain and who do not have evidence of peripheral tissue necrosis.	RED-RED All remaining patients should be reviewed in response to new contra-indications.
Eplerenone 25mg and 50mg tablets (*Inspra*)	For use as an adjunct in stable patients with left ventricular dysfunction (LVD) with evidence of heart failure (HF) following myocardial infarction.	GREEN Approved for inclusion on the Joint Formulary for this indication. Should be considered second line in those intolerant to spironolactone.
Eplerenone 25mg and 50mg tablets (*Inspra*)	For use as an adjunct in chronic mild heart failure with left ventricular ejection fraction $\leq$ 30%	GREEN Approved for inclusion on the Joint Formulary for this indication. Should be considered second line in those intolerant to spironolactone.
Flutter oscillating positive expiratory pressure (PEP) device	For the alleviation of mucus producing conditions such as atelectasis, bronchitis, bronchiectasis, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and asthma.	AMBER - should only be prescribed following patient assessment and recommendation of a PEP device by a specialist respiratory physiotherapist.
Ketorolac 0.5% eye drops (*Acular*)	For the prophylaxis and reduction of inflammation and associated symptoms following ocular surgery	AMBER without shared care. Included on the Joint Formulary
Lisdexamfetamine 30mg/50mg/70mg capsule (*Elvanse*)	For use in the treatment of Attention Deficit Hyperactivity Disorder in children $\geq$ 6 years when response to methylphenidate is considered inadequate.	AMBER with shared care. Approved for inclusion on the Joint Formulary
Lixisenatide 10microgram/ 20microgram injection (*Lyxumia*)	For use as an adjunct to existing oral hypoglycaemic and/or insulin therapy in type 2 diabetes mellitus (DM) where glycaemic control is inadequate.	GREEN Approved for inclusion on the Joint Formulary
Methylnaltrexone bromide injection	For the treatment of opioid induced	AMBER without shared care.

(*Relistor*)	constipation in adult patients who are receiving palliative care where response to usual laxative therapy has not been sufficient.	Approved for inclusion on the Joint Formulary Subject to specialist initiation by the St Barnabus medical team only
Nepafenac 1mg/ml eye drops (*Nevanac*)	For the prevention and treatment of pain and inflammation following cataract surgery. For the reduction in risk of postoperative macular oedema associated with cataract surgery in diabetic patients.	RED-RED Not approved for Joint Formulary inclusion
Racecadotril sachets 10mg/30mg (*Hidrasec Infant*/*Hidrasec Children*) and capsules 100mg (*Hidrasec*)	For the treatment of acute diarrhoea	RED-RED Not approved for Joint Formulary inclusion
Strontium ranelate 2g sachets (*Protelos*)	For the treatment of postmenopausal osteoporosis and osteoporosis in men at increased risk of fracture	AMBER without shared care Included in the Joint Formulary
Tobramycin dry powder for inhalation (*TOBI Podhaler*)	For the suppression of chronic pulmonary infection caused by *P.aeruginosa* in adults and children aged 6 years and older with CF.	AMBER subject to shared care Approved for inclusion on the Joint Formulary

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.

RAPID DRUG ASSESSMENT: *EPLERENONE 25MG AND 50MG TABLETS FOR LEFT VENTRICULAR DYSFUNCTION AND HEART FAILURE*

Eplerenone (*Inspra*) is the only aldosterone antagonist licensed for use in stable patients with left ventricular dysfunction (LVD) (LVEF ≤ 40%) with clinical evidence of heart failure (HF) following recent myocardial infarction. PACEF reviewed the evidence for eplerenone for this indication in August 2007 and the drug was approved for use and designated AMBER. (see *PACE Bulletin* Vol 1 No 4 (September 2007)). Subsequently, eplerenone (*Inspra*) has also gained a marketing authorisation for left ventricular dysfunction (LVEF ≤ 30%) and heart failure (NYHA II).

Evidence to support this extension to the marketing authorisation came from a single, large, placebo-controlled clinical study known as EMPHASIS-HF (Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms). 2737 patients aged ≥ 55 years with LVEF≤30% (or LVEF ≤35% with a QRS interval >130ms) and a recent hospitalisation for a cardiovascular reason (within the last six months) were randomised to either eplerenone 25mg daily titrating up to 50mg daily within 4 weeks or matching placebo. At baseline, patients were receiving treatment with optimal target or maximally-tolerated doses of an angiotensin-converting enzyme inhibitor and/or angiotensin-receptor blocker and a beta-blocker (unless contra-indicated). The primary endpoint was a composite of death from cardiovascular causes or hospitalisation for heart failure. Eplerenone was found to reduce the risk of cardiovascular mortality and morbidity in these patients with a number needed to treat estimated at 19 to prevent one event (i.e. death from CV causes or hospitalisation from HF).

Rates of gynaecomastia, impotence and breast pain associated with eplerenone are less than those associated with spironolactone and comparable to placebo. A cost comparison reveals the following:

Drug	Dose	Cost for 28 days treatment
Eplerenone (*Inspra*) 25mg or 50mg tablets	25 to 50mg once daily	£42.72
Spironolactone tablets	25 to 50mg once daily	£1.37 to £1.88

PACEF Recommendation:
Having reviewed the evidence for use in left ventricular dysfunction (LVEF ≤ 30%) and heart failure (NYHA II), PACEF have approved eplerenone (*Inspra*) for this indication. NICE have previously recommended spironolactone for patients with HF who remain moderately to

severely symptomatic despite optimal treatment with a diuretic, ACEI and BB. Within this context, eplerenone should be reserved for those intolerant to spironolactone. Designation: GREEN to allow GP initiation where appropriate.
Previously, eplerenone (*Inspra*) has also been approved for use post-MI (initiated within 3 to 14 days of the event) for patients with signs and symptoms of heart failure and left ventricular systolic dysfunction. Within this context, eplerenone has been re-classified from AMBER to GREEN; it should be used second line in those intolerant to spironolactone.
Intensive initial monitoring is required; renal function and serum potassium should be monitored before and during treatment. Serum potassium should be measured within the first week of, and a month after, starting therapy or dose adjustment and periodically thereafter.

NEW DRUG ASSESSMENT: *NEPAFENAC 1MG/ML EYE DROPS (NEVANAC)*

Nepafenac 1mg/ml eye drops (*Nevanac*) are a new ocular NSAID formulation with marketing authorisations for:

- the prevention and treatment of pain and inflammation following cataract surgery.
- the reduction in risk of postoperative macular oedema associated with cataract surgery in diabetic patients.

The evidence for use in diabetic patients is from a randomised, multi-centre, double-masked, vehicle-controlled, parallel study in type 1 and type 2 diabetic patients needing cataract surgery. 251 adult patients with type 1 or type 2 diabetes and non-proliferative diabetic retinopathy requiring cataract surgery were randomised to either nepafenac eye drops or the vehicle. All patients received prednisolone acetate 1mg/ml eye drops for 2 weeks post-surgery or longer if necessary to treat anterior segment inflammation. The proportion of patients who developed postoperative macular oedema was significantly lower in the nepafenac group (3.2%) than in the vehicle group (17%). No data is available comparing nepafenac eye drops with any other NSAID eye drop for this indication (e.g. ketorolac 0.5% eye drops).

Historically, local ophthalmologists have used ketorolac 0.5% eye drops (*Acular*) within this context. *Acular* holds a general marketing authorisation for the prophylaxis and reduction of inflammation and associated symptoms following ocular surgery, but does not hold the specific marketing authorisation around reduction of risk of macular oedema in diabetic patients after cataract surgery.

A cost comparison of the two products reveals that nepafenac eye drops are five times the price of ketorolac eye drops:

Drug	Pack size	NHS price per bottle
Nepafenac 1mg/ml eye drops (*Nevanac*)	5ml bottle	£14.92
Ketorolac 0.5% eye drops (*Acular*)	5ml bottle	£3.00

PACEF Recommendation:
In the absence of comparative evidence, PACEF were unable to determine whether nepafenac 1mg/ml eye drops (*Nevanac*) were a genuine advance on existing ocular NSAID formulations such as ketorolac 0.5% eye drops (*Acular*). As a result of this, ketorolac 0.5% eye drops (*Acular*) remain the preferred ocular NSAID and are designated GREEN for the prophylaxis and reduction of inflammation and associated symptoms following ocular surgery. Nepafenac 1mg/ml eye drops (*Nevanac*) are designated RED-RED.

NEW DRUG ASSESSMENT: *RACECADOTRIL SACHETS AND CAPSULES (HIDRASEC)*

Racecadotril (*Hidrasec*) is an anti-hypersecretory agent that has been used for several years in Europe for the treatment of watery diarrhoea. It acts by stimulating intestinal absorption but does not affect transit time or motility. It holds a marketing authorisation for use as an adjunct to oral rehydration in acute diarrhoea in adults and children aged over three months of age.

Supporting evidence for its use in children comes from a meta-analysis (MA) of nine paediatric studies conducted in South America, India, Spain and France. This MA showed that racecadotril plus an oral rehydration salt solution (ORS) significantly improves recovery rate and reduces both volume and frequency of diarrhoea compared to ORS solution alone when used in children. The evidence base for use in adults comes from two trials comparing racecadotril against loperamide; of these, one trial was based in South American and African countries and the other in France. These trials indicate that racecadotril is similar in efficacy to loperamide in terms of reduction in duration of diarrhoea and number of stools; it also causes fewer adverse effects than loperamide, specifically, it causes fewer problems with constipation.

A cost comparison reveals that racecadotril is more expensive than most alternative treatment options:

Drug	Daily dose range	Cost (£)
Racecadotril 10mg sachets (*Hidrasec Infant*)	10mg three times daily	£8.42 (20)
Racecadotril 30mg sachets (*Hidrasec Children*)	30mg three times daily	£8.42 (20)
Racecadotril 100mg capsules (*Hidrasec*)	100mg three times daily	£8.42 (20)
Oral rehydration solutions		
Dioralyte	1 sachet after every loose stool	£6.72 (20)
Electrolade	1 sachet after every loose stool	£4.99 (20)
Anti-motility drugs		
loperamide	4mg initially then 2mg after each loose stool to a maximum of 8 in 24 hours	£0.94 (30)
Co-phenotrope	4 tablets initially then 2 tablets every 6 hours	£10.74 (100)
Codeine phosphate 30mg	1 tablet 3-4 times daily	£1.49 (28)

PACEF Recommendation:
It is unclear where racecadotril (*Hidrasec*) fits into current UK practice. The majority of children in the UK recover from diarrhoea without treatment or with simple ORS therapy. By contrast, acute diarrhoea has much more impact in other parts of the world where it can pose a serious threat, particularly to young children. A significant proportion of the trial evidence for racecadotril derives from countries in which more aggressive therapy of acute diarrhoea can undoubtedly save lives. PACEF is also mindful of the additional cost of racecadotril compared to well established and effective alternatives. Neither the Scottish Medicines Consortium nor the All Wales Medicines Strategy Group have approved the product for use. A recent review by the *Drug and Therapeutics Bulletin* (May 2013) emphasized that this is a disease area in which the majority of cases are self-limiting and symptoms resolve without drug treatment. Taking all of this into consideration, racecadotril sachets 10mg/30mg (*Hidrasec Infant/ Hidrasec Children*) and capsules 100mg (*Hidrasec*) are designated RED-RED and have not been approved for *Joint Formulary* inclusion.

NEW DRUG ASSESSMENT: *LISDEXAMFETAMINE DIMESYLATE CAPSULES 30MG/50MG/70MG (ELVANSE)*

Lisdexamfetamine (LDX) dimesylate (*Elvanse*) is a pharmacologically inactive pro-drug which is hydrolysed in the body to the CNS stimulant, dexamfetamine. It has a marketing authorisation for use in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children ≥ 6 years when response to methylphenidate (MPH) is considered clinically inadequate.

Evidence for use of LDX comes from 3 pivotal trials only one of which has been published. The published data covers a short-term (7 week), double blind, randomised controlled trial (RCT) in which LDX in doses of 30mg, 50mg and 70mg a day was compared to a range of doses of MPH in an osmotic release oral system and to placebo. The effectiveness of each treatment option was evaluated in terms of the ADHD-RS-IV (an ADHD rating scale which measures the core symptoms of ADHD) and the Clinical Global Impressions-Improvement (CGI-I) ratings. Of 336 patients randomized, only 196 completed the study. LDX emerged from this comparison as significantly more effective than both MPH and placebo. The most commonly reported adverse effects with LDX were decreased

appetite, headache and insomnia. Additional evidence considered by PACEF included a poster presentation and data on file from the manufacturer which compared LDX with atomoxetine.

Treatment with LDX must be initiated by a specialist in childhood and/or adolescent behavioural disorders. Diagnosis is made according to DSM-IV or ICD-10 criteria and must be based on a complete history and evaluation of the patient. LDX is a once daily preparation in comparison to the three to four times daily dosage required for dexamfetamine. The starting dose is 30mg in the morning which can be increased by 20mg increments at approximate weekly intervals up to a maximum of 70mg daily. Treatment must be stopped if symptoms do not improve over one month or if symptoms deteriorate or if intolerable side-effects develop.

A cost comparison with other alternative treatments reveals that LDX is significantly more costly than methylphenidate preparations and comparable in price with atomoxetine (*Strattera*), another second line option:

Drug	**Daily dose**	**Cost (28 days)**
Lisdexamfetamine 30mg capsule (*Elvanse*)	**30mg once daily in the morning**	**£58.24**
Lisdexamfetamine 50mg capsule (*Elvanse*)	**50mg once daily in the morning**	**£68.60**
Lisdexamfetamine 70mg capsule (*Elvanse*)	**70mg once daily in the morning**	**£83.16**
Dexamfetamine 5mg tablets (generic)	5mg three to four times a day	£56.70 to £75.60
Methylphenidate 18mg MR tablets (*Concerta XL*)	18mg once daily in the morning	£29.11
Methylphenidate 27mg MR tablets (*Concerta XL*)	27mg once daily in the morning	£34.36
Methylphenidate 36mg MR tablets (*Concerta XL*)	36mg once daily in the morning	£39.62
Methylphenidate 10mg MR capsule (*Equasym XL*)	10mg once daily in the morning	£23.33
Methylphenidate 20mg MR capsule (*Equasym XL*)	20mg once daily in the morning	£28.00
Methylphenidate 30mg MR capsule (*Equasym XL*)	30mg once daily in the morning	£32.67
Methylphenidate 5mg SR capsule (*Medikinet XL*)	5mg once daily	£22.44
Methylphenidate 10mg SR capsule (*Medikinet XL*)	10mg once daily	£22.44
Methylphenidate 20mg SR capsule (*Medikinet XL*)	20mg once daily	£26.90
Methylphenidate 30mg SR capsule (*Medikinet XL*)	30mg once daily	£31.42
Methylphenidate 40mg SR capsule (*Medikinet XL*)	40mg once daily	£53.87
Atomoxetine 10mg capsule (*Strattera*)	10mg once daily in the morning	£62.46
Atomoxetine 18mg capsule (*Strattera*)	18mg once daily in the morning	£62.46
Atomoxetine 25mg capsule (*Strattera*)	25mg once daily in the morning	£62.46
Atomoxetine 40mg capsule (*Strattera*)	40mg once daily in the morning	£62.46
Atomoxetine 60mg capsule (*Strattera*)	60mg once daily in the morning	£62.46
Atomoxetine 80mg capsule (*Strattera*)	80mg once daily in the morning	£83.28
Atomoxetine 100mg capsule (*Strattera*)	100mg once daily in the morning	£83.28

PACEF Recommendation:

PACEF were concerned about the paucity of published data with lisdexamfetamine (*Elvanse*) and the lack of data against the obvious comparator, dexamfetamine. Nonetheless, the small scale, short-term published trial that was reviewed shows that LDX has some promise as a potential option when response to MPH is inadequate. The once daily dosage regime compared to three to four times daily with conventional dexamfetamine was also felt to be potentially advantageous as it does not require the child to take the mid-day dose of drug that is likely to become a schedule 2 controlled drug into school with them. The need for specialist assessment prior to initiation, the second line positioning after MPH, the possible need for dose titration, the need for cessation of therapy if response is insufficient or the drug is poorly tolerated and the need for ongoing monitoring all suggest the need for incorporation into the ADHD shared care guidelines. As a result of this, lisdexamfetamine (*Elvanse*) is designated AMBER with shared care. It should only be used in children aged 6 and over where the

response to MPH is considered clinically inadequate. It is approved for inclusion in the *Joint Formulary* subject to these criteria.

NEW DRUG ASSESSMENT: *LIXISENATIDE 10 MICROGRAM/20MICROGRAM INJECTION (LYXUMIA)*

Lixisenatide (*Lyxumia*) is the third glucagon-like peptide-1 (GLP-1) or incretin mimetic to be granted a UK marketing authorisation. It is licensed for use as an adjunct to existing oral hypoglycaemic and/or insulin therapy in type 2 diabetes mellitus (DM) where glycaemic control is inadequate.

The supporting evidence reviewed by PACEF comes from a series of clinical trials, known as the GET-GOAL studies, not all of which have been fully published. Results from these studies confirm that lixisenatide produces a significant reduction in HbA1c levels in comparison to placebo when added on to existing type 2 diabetic therapies including basal insulin. Comparative data against existing treatment options is limited. The only published trial is a one month pharmacodynamic study comparing lixisenatide with liraglutide 1.8mg (a dose not recommended by NICE) in 148 patients inadequately controlled on metformin. The main outcome of the trial was the effect on postprandial glucose (PPG) levels; lixisenatide was found to reduce PPG significantly more than liraglutide. PACEF were uncertain of the significance of this finding. There is a link between reduction in PPG and reduction in HbA1c levels, but PPG is not normally used as a measure on its own to assess how well diabetes is controlled.

In common with other incretin mimetics, lixisenatide causes gastro-intestinal adverse effects with around a quarter of patients reporting nausea and 7-9% reporting vomiting and diarrhoea. Comparative tolerability data derived from the pharmacodynamic trial detailed above reported GI adverse effects in 36% of lixisenatide patients and 46% of liraglutide patients. However the dose of liraglutide was the higher dose of 1.8mg which is associated with a higher incidence of adverse effects than the NICE recommended dose of 1.2mg.

A cost comparison reveals that lixisenatide is competitively priced, costing less than either of the two more established GLP-1 mimetics, exenatide and liraglutide:

Drug	Daily dose	Annual Cost (£) pa
Lixisenatide 20 microgram injection (*Lyxumia*)	**20mcg daily**	**£703.82**
Exenatide 5 microgram injection (*Byetta*)	5mcg twice daily	£818.88
Exenatide 10 microgram injection (*Byetta*)	10mcg twice daily	£818.88
Exenatide 2mg prolonged release injection (*Bydureon*)	2mg once weekly	£956.30
Liraglutide 6mg/ml injection (*Victoza*)	1.2mg once daily	£956.30

PACEF Recommendation:
PACEF are persuaded that lixisenatide (*Lyxumia*) is an effective GLP-1 mimetic that provides a potential alternative to the already available products, exenatide (*Byetta*) and liraglutide (*Victoza*). However, despite the range of studies available from launch, not all of the relevant data is fully published, many of the studies are short-term (24 weeks) and convincing comparative data against other GLP-1 mimetics is sparse. There is a suggestion from a single short-term study that lixisenatide may be more effective and better tolerated than liraglutide, although it would be premature to draw such a conclusion from such limited evidence. PACEF were also concerned about the lack of long-term safety data with the product, particularly in light of the recently announced European Medicines Agency (EMA) safety review of all of the GLP-1 mimetics due to possible increased risks of pancreatitis and pre-cancerous changes associated with these drugs. As a result of this, lixisenatide 10microgram/20microgram injection (*Lyxumia*) is designated GREEN subject to NICE criteria for the treatment of type 2 DM. It is also approved for inclusion in the *Joint Formulary*. The better established GLP-1 mimetics, exenatide and liraglutide continue to be the agents of choice, particularly liraglutide as it has just lost its 'black triangle status'. Despite its lower cost, lixisenatide cannot be supported as the first line GLP-1 mimetic of choice at this stage as too many unanswered questions remain about its long-term safety and clinical efficacy in comparison to the more

established agents. PACEF will revisit this assessment in the coming months in order to ensure that any additional information emerging from the GET GOAL studies is fully evaluated.

NICE TECHNOLOGY APPRAISAL 276: *COLISTIMETHATE SODIUM AND TOBRAMYCIN DRY POWDERS FOR INHALATION FOR TREATING PSEUDOMONA LUNG INFECTION IN CYSTIC FIBROSIS* (MARCH 2013)

Tobramycin dry powder for inhalation (DPI) is recommended as an option for treating chronic pulmonary infection caused by *Pseudomonas aeruginosa* in people with cystic fibrosis (CF) only if:

- nebulised tobramycin is considered an appropriate treatment, that is, when colistimethate sodium is contraindicated , is not tolerated or has not produced an adequate clinical response and
- the manufacturer provides tobramycin DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

Colistimethate sodium DPI is recommended as an option for treating chronic pulmonary infection caused by *P.aeruginosa* in people with CF only if:

- they would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulised form and thus tobramycin therapy would otherwise be considered and
- the manufacturer provides colistimethate sodium DPI with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

Notes

P. aeruginosa is the most frequent cause of lung infection in people with cystic fibrosis; around 38% of UK patients had a chronic pseudomonas infection in 2010. The length and quality of life of people with CF are thought to be strongly influenced by the degree to which *P.aeruginosa* infection can be eradicated. However, chronic *P.aeruginosa* infection is rarely completely eradicated. Management of *P.aeruginosa* lung infection in CF involves treatment with antibiotics, given in hospital, at home or in a combination of these settings. The aims of antibiotic treatment are to: (1) eradicate intermittent acute *P.aeruginosa* lung infections; (2) suppress *P.aeruginosa* with long-term treatment in patients who have become chronically infected; and (3) to treat acute exacerbations in patients chronically infected. Current treatment options include inhaled antibiotics (nebulised colistimethate sodium or tobramycin) and oral or intravenous antibiotics.

First line treatment

First line treatment for chronic *P. aeruginosa* lung infection routinely starts with nebulised colistimethate sodium (unless contra-indicated), this choice is largely based on cost. If there is no response, unacceptable adverse events or an excessive number of acute exacerbations or a loss of lung function, treatment is switched routinely to nebulised tobramycin.

Colistimethate sodium DPI

Colistimethate sodium DPI (*Colobreathe*) is a formulation of colistimethate sodium supplied as hard capsules for use in an inhaler. It is indicated for the management of chronic pulmonary infections caused by *P.aeruginosa* in patients with CF aged 6 years and older. The recommended dose is 1 capsule (125mg) to be inhaled twice daily using the *Turbospin* inhaler device (a breath activated, reuseable DPI). The price for a 28 day pack including the *Turbospin* inhaler is £968. The cost will be reduced by the patient access scheme. Trial evidence suggests that colistimethate sodium DPI is non-inferior to nebulised tobramycin, but more expensive. There is no trial evidence comparing colistimethate sodium DPI with the preferred comparator nebulised colistimethate sodium (preferred first line therapy).

Tobramycin DPI

Tobramycin DPI (*TOBI Podhaler*) is a formulation of tobramycin supplied as hard capsules for use with an inhaler. It is indicated for the suppression of chronic pulmonary infection caused by *P.aeruginosa* in adults and children aged 6 years and older with CF. The recommended dosage is 112mg (4x28mg capsules) twice daily for 28 days using the Podhaler device in alternating cycles of 28 days on and 28 days off. The price for 28 days' treatment assuming 8 capsules each day is

£1,790. The cost will be reduced by the patient access scheme. Tobramycin DPI is non-inferior to nebulised tobramycin, but more expensive.

PACEF Recommendation:
Both colistimethate sodium DPI (*Colobreathe*) and tobramycin DPI (*TOBI Podhaler*) are approved for inclusion in the Joint Formulary. First line treatment for chronic *P. aeruginosa* lung infection will continue to be nebulised colistimethate sodium (unless contra-indicated). If there is no response, unacceptable adverse events or an excessive number of acute exacerbations or a loss of lung function, treatment should be switched to nebulised tobramycin. Colistimethate sodium DPI (*Colobreathe*) and tobramycin DPI (*TOBI Podhaler)* will only be considered within NICE criteria and subject to the patient access scheme. Both products are designated AMBER subject to the development of shared care guidelines.

NICE TECHNOLOGY APPRAISAL 277: *METHYLNALTREXONE FOR TREATING OPIOID – INDUCED BOWEL DYSFUNCTION IN PEOPLE WITH ADVANCED ILLNESS RECEIVING PALLIATIVE CARE (TERMINATED APPRAISAL)* (MARCH 2013)

NICE is unable to recommend the use in the NHS of methynaltrexone for treating opioid-induced bowel dysfunction in people with advanced illness receiving palliative care because no evidence submission was received from the manufacturer.

Notes

PACEF originally assessed methylnaltrexone bromide injection (*Relistor*) in March 2009 (published in *PACE Bulletin* Vol 3 No 4 (April 2009)). Methylnaltrexone is a peripherally acting mu-opioid receptor antagonist and is licensed for the treatment of opioid induced constipation in adult patients who are receiving palliative care where response to usual laxative therapy has not been sufficient. There is limited evidence to suggest that methylnaltrexone alleviates opioid–induced constipation without compromising analgesia. The drug appears to be well tolerated with the most common adverse effect being abdominal pain and flatulence, although there is no long term safety data. The manufacturer recommends that treatment should be restricted to patients with advanced disease and limited life expectancy and should be for a limited period (not exceeding three months). Methylnaltrexone is much more expensive than standard laxatives (about twenty five times the cost), however, the higher cost could be offset by prevented hospitalisations. The judicious use of methylnaltrexone may enable some patients to remain at home during the final stages of their illness.

The manufacturer of methylnaltrexone (Relistor), TMC Pharma Services, did not make an evidence submission to NICE for this appraisal as they are only holding the European Marketing Authorisation on a temporary basis while the product owner finds a permanent European partner.

PACEF Recommendation:
PACEF have previously agreed a limited role for methylnaltrexone bromide injection (*Relistor*) in response to specialist advice from a palliative care specialist and are inclined to continue to support this arrangement. As a result of this, methylnaltrexone bromide injection (*Relistor*) continues to be designated AMBER. It should only be prescribed by a GP in response to specialist advice from a palliative care specialist; there is no requirement for a shared care guideline.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) *DRUG SAFETY UPDATE (APRIL 2013)*

Cilostazol (*Pletal*) risk of cardiovascular and bleeding events – indication restricted to second-line treatment and contraindicated with some cardiovascular conditions and medicines

Cilostazol (*Pletal*) is a phosphodiesterase type 3 inhibitor indicated for the improvement of walking distances in patients with intermittent claudication who do not have rest pain and who do not have evidence of peripheral tissue necrosis. A review of cilostazol by the MHRA was triggered by reports of adverse reactions, mainly cardiac and haemorrhagic.

The most common adverse reactions reported with treatment are relatively minor headaches, diarrhoea, palpitations, and dizziness. However, cilostazol has been shown to increase heart rate by about 5 to 7 beats per minute and this may put some patients at increased risk of cardiac events. Contraindications to treatment have been revised to include unstable angina, recent myocardial infarction or coronary intervention (within 6 months), history of severe tachyarrhythmia and those receiving two or more antiplatelet or anticoagulant agents.

A recent phase 4 long term safety study known as CASTLE had a primary endpoint of all-cause mortality. The trial was terminated early due to a low event rate and provided some reassurance of cardiac safety. However, a review of bleeding risk showed that there was a high frequency of bleeding events when cilostazol was combined with both clopidogrel and aspirin although this was not observed with cilostazol alone or when combined with either clopidogrel or aspirin alone.

The MHRA have issued the following advice to healthcare professionals

- Cilostazol is restricted to second-line treatment where lifestyle modifications (e.g. smoking cessation and exercise regimens) and other appropriate interventions have failed to provide sufficient improvement. Lifestyle changes should continue during treatment.
- Cilostazol is contraindicated in patients:
  - with unstable angina, recent myocardial infarction or coronary intervention (within 6 months)
  - with a history of severe tachyarrhythmia
  - receiving two or more antiplatelet agents or anticoagulants.
- Advise patients to take cilostazol 30 minutes before breakfast and evening meal.
- Reassess patients after 3 months of starting cilostazol and consider stopping treatment if there is no clinically relevant improvement in walking distance.
- A dose reduction to 50 mg twice a day is recommended when cilostazol is taken in combination with any of the following: erythromycin; clarithromycin; ketoconazole; itraconazole; omeprazole; or any strong inhibitors of CYP3A4 or CYP2C19.
- Reassess patients currently receiving long term treatment with cilostazol at a routine appointment in order to advise on treatment continuation, dose change or cessation.

PACEF Recommendation:
Prescribers are reminded that cilostazol (*Pletal*) is not recommended by NICE to improve walking distances in those with intermittent claudication. However, patients who were receiving the therapy for this indication prior to the publication of NICE TA 223 in May 2011 are able to continue with therapy until they or their clinician consider it appropriate to stop. PACEF have designated cilostazol 50mg and 100mg tablets (*Pletal*) as RED-RED for this indication and no new patients should be started on therapy. Current prescribing data suggests that there are a small number of patients in Lincolnshire continuing to be prescribed the drug. Prescribers are urged to review all patients according to MHRA criteria with a view to stopping therapy in those who now have a contra-indication to treatment.

Strontium ranelate (*Protelos*) risk of serious cardiac disorders – restricted indications, new contra-indications and warnings

A review of available safety data for strontium ranelate (*Protelos*) has raised concern about its cardiovascular safety beyond the already recognised risk of venous thromboembolism. The MHRA have issued the following advice to healthcare professionals:

- The use of strontium ranelate is now restricted to treatment of severe osteoporosis in postmenopausal women at high risk of fracture or in men at increased risk of fracture.
- Treatment should only be initiated by a physician with experience in the treatment of osteoporosis; the decision to prescribe strontium ranelate should be based on an assessment of the individual patient's overall risk.
- Strontium ranelate should not be used in patients with ischaemic heart disease, peripheral arterial disease or cerebrovascular disease or in patients with a history of these conditions or in patients with uncontrolled hypertension.
- Prescribers are advised to assess the patient's risk of developing cardiovascular disease before starting treatment and thereafter at regular intervals.

- Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking) should only be treated with strontium ranelate after careful consideration.
- Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease, cerebrovascular disease, or if hypertension is uncontrolled.
- Healthcare professionals should review patients at a routine appointment and consider whether or not to continue treatment.

PACEF Recommendation:
As a result of these emerging safety concerns, strontium ranelate granules (*Protelos*) are no longer considered appropriate for GP initiation and have been reclassified as AMBER with shared care. New patients should only be initiated on strontium ranelate on the advice of a specialist with experience in the treatment of osteoporosis and within the context of a shared care guideline. To this end, the Lincolnshire SCG is currently in development. Existing patients should be reviewed in accordance with MHRA guidance at their next routine appointment and consideration given to stopping therapy where a contra-indication is identified or where the risk of ongoing therapy is thought to outweigh the potential benefits.

Recent drug name confusion

The MHRA are now aware of recent medication errors resulting from patients being prescribed or supplied with the wrong medicine due to confusion between similarly named products. Recent examples include:

- Mercaptamine and mercaptopurine
- Sulfadiazine and sulfasalazine
- Risperidone and ropinirole
- zuclopenthixol decanoate and zuclopenthixol acetate

The MHRA advise that health care professionals should remain vigilant when dealing with medication names which either look alike when written down or sound alike.

PACEF Comment:
Many prescribers will be aware of the events of last summer where a number of patient-related incidents occurred in Lincolnshire as a result of zuclopenthixol acetate injection (*Clopixol Acuphase*) being prescribed, dispensed and administered where zuclopenthixol decanoate injection (*Clopixol*) was intended. Initially the risk of potential confusion was highlighted to all prescribers through the *PACE Bulletin* (Vol 6 No 12 (August 2012)). Following a multi-agency review of the incidents, work is now in progress within Lincolnshire to change the provision of depot antipsychotic drugs so that all responsibility for the prescribing, supply and administration remains with specialist mental health services.

NEW TREATMENT ALGORITHM: *FLUTTER OSCILLATING POSITIVE EXPIRATORY PRESSURE DEVICE*

(Reprinted from original assessment published in *PACE Bulletin* Vol 7 No 4 (February 2013))

Flutter is an oscillating positive expiratory pressure (PEP) device which may be of use in the alleviation of mucus producing conditions such as atelectasis, bronchitis, bronchiectasis, cystic fibrosis (CF), chronic obstructive pulmonary disease (COPD) and asthma. It is a pipe shaped device with a mouthpiece at one end and a perforated plastic cover at the other; inside is a high density steel ball which rests within a plastic circular cone. Before exhalations the steel ball blocks the conical canal of the device. The ball is moved by a combination of the pressure of exhaled air, the force of gravity on the ball and the angle of the cone. During exhalation the steel ball rolls and bounces up and down, creating an opening and closing cycle within the valve like device which repeats many times during each exhalation. The oscillations in expiratory pressure and airflow that are created by the device result in vibrations occurring within the airways. This can be felt as a fluttering sensation, hence the name given to the device. The result of the vibrations is to loosen mucus from the airway walls. *Flutter* therapy is complete when no further mucus can be expectorated. Frequency of use and

duration of each session varies with each patient, but usually the whole process takes between 5 to 15 minutes and is repeated twice daily, once in the morning and once in the late afternoon or evening.

PACEF Recommendation

There is evidence to suggest that oscillating PEP devices like *Flutter* are helpful in enabling patients with mucus producing conditions to clear secretions, increase expectorated sputum volume and improve respiratory function. This may, in turn, reduce the risk of respiratory infection and improve the patient's general health and wellbeing. However, oscillating PEP devices are not easy to use effectively and patients must be trained in their use by specialist physiotherapy services. The patient must also have tried and gained insufficient benefit from alternative techniques such as assisted controlled breathing (ACBT). As a result of this, the *Flutter* PEP device is designated AMBER. It should only be prescribed following patient assessment and recommendation of a PEP device by a specialist respiratory physiotherapist. It should not be prescribed in response to a direct patient request to a GP as physiotherapist assessment and training is crucial to ensure selection of appropriate patients and maximum benefit from the device. The treatment algorithm provided below details the place in therapy of *Flutter* as defined by the specialist physiotherapists who will in certain circumstances request that the *Flutter* device should be prescribed by the patient's GP.

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Clinical pathway for use of Flutter Oscillating Positive Expiratory Pressure Device