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 8; Number 1 **January 2014**

What's new this month?

- **PACEF have evaluated dapoxetine 30mg and 60mg tablets (*Priligy*) within the context of available evidence and in comparison with a range of unlicensed alternatives and have concluded that prescribing of any treatment for premature ejaculation on the NHS cannot be justified in an environment in which competing health needs of much greater urgency need to be prioritised. As a result of this, dapoxetine 30mg and 60mg tablets (*Priligy*) are designated RED-RED and should not be prescribed. Alternative unlicensed therapies, such as selective serotonin reuptake inhibitors (SSRIs), should not be initiated in new patients for this indication; existing patients can continue to receive prescriptions until they or their clinician consider it appropriate to stop (see page 5).**
- **Nicotine 2.5mg orodispersible film (*NiQuitin Strips Mint*) are designated RED-RED and should not be prescribed, even if requested by local specialist smoking cessation services. Where a rapid acting nicotine formulation is indicated, *Nicorette QuickMist* oromucosal spray has previously been evaluated by PACEF and designated GREEN (see page 8).**
- **Following the withdrawal of timolol 0.1% eye gel (*Nyogel*), PACEF have approved timolol 0.25% and 0.5% ophthalmic gel-forming solution (*Timoptol-LA*) and timolol 0.1% unit dose eye gel (*Tiopex*) (preservative free) as replacement preparations. All of these products are designated AMBER without shared care and approved for use on the *Lincolnshire Joint Formulary* (see page 9).**
- **All varicella zoster vaccine (*Zostavax*) required for the national vaccination programme can be ordered free of charge from ImmForm. Individual FP10 prescriptions should not be submitted to the NHSBSA PPD as claims for reimbursement. Practices that have inadvertently over-claimed for *Zostavax* from the PPD can rectify the claim by emailing the NHS BSA giving details of what they have claimed, when they submitted the claim and what they wish to rectify; any necessary changes to practice reimbursement can then be made by the PPD (see page 9).**
- ***Laxido Orange* and *Molaxole* are equivalent macrogol (polyethylene glycol) osmotic laxative formulations and are significantly lower in cost than *Movicol*. As a result of this, both *Laxido Orange* and *Molaxole* are designated GREEN and approved for inclusion on the *Joint Formulary* (see page 10).**
- **Lercanidipine 10mg and 20mg tablets are available as low cost generics and are approved for inclusion in the *Joint Formulary* as a potential first line alternative to amlodipine for the treatment of hypertension subject to NICE guidance; designation GREEN (see page 10).**
- ***Filnarine SR* is a new modified release morphine preparation even lower in cost than *Morphgesic* and *Zomorph*. It is available in 10mg, 30mg, 60mg and 100mg strengths and is approved for inclusion in the *Joint Formulary*. Designation: GREEN (see page 11).**
- **The *Canesten Combi Pack* (containing clotrimazole 500mg pessary plus 2% cream (10g) has been approved for inclusion in the *Joint Formulary* on the basis that the individual components prescribed separately are more costly. Designation GREEN (see page 11).**
- **There are now four ethinylestradiol 30 microgram /levonorgestrel 150 microgram combined oral contraceptive tablet formulations available in the UK: *Levest*, *Microgynon 30*, *Ovranette* and *Rigevidon*. Of these, *Levest* and *Rigevidon* are lower cost and designated GREEN; both products are approved for inclusion in the *Joint***

***Formulary*. In comparison, *Microgynon 30 and Ovranette* are more expensive and should no longer be initiated in new patients; *Microgynon 30 and Ovranette* are designated RED-RED and have been removed from the *Joint Formulary* (see page 11).**

- **PACEF are in support of the review of all patients currently taking modified release quetiapine tablets (such as *Seroquel XL*) with the object of moving as many people as possible to an equivalent dose of immediate release quetiapine tablets (see page 11).**
- **LPFT have asked us to clarify that aripiprazole is designated RED for the treatment of moderate to severe manic episodes in adolescents with bipolar disorder, but continues to be designated AMBER without shared care for the treatment of schizophrenia and the treatment and prevention of mania (see page 14).**

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SUMMARY OF PACEF DECISIONS: *DECEMBER 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Amlodipine 5mg and 10mg tablets (generic)	For the treatment of hypertension and the prophylaxis of angina	GREEN First line option in hypertension subject to NICE guidance. Included in the *Lincolnshire Joint Formulary*.
Aripiprazole 5mg and 10mg tablets (Abilify) Aripiprazole 10mg orodispersible tablets (Abilify Orodispersible) Aripiprazole 1mg/ml oral solution (Abilify Oral Solution)	For the treatment of schizophrenia. For the treatment and recurrence prevention of mania	AMBER without shared care. Included in the *Joint Formulary* for this indication.
Aripiprazole 5mg and 10mg tablets (Abilify) Aripiprazole 10mg orodispersible tablets (Abilify Orodispersible) Aripiprazole 1mg/ml oral solution (Abilify Oral Solution)	For the treatment of moderate to severe manic episodes in bipolar I disorder in adolescents aged 13 and older.	RED Approved for inclusion in the *Joint Formulary* for this indication. .
Bosutinib 100mg and 500mg tablets (*Bosulif*)	For the treatment of chronic, accelerated or blast phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML) previously treated with one or more tyrosine kinase inhibitors and where imatinib, nilotinib and dasatinib are not appropriate.	RED Included in the *Lincolnshire Joint Formulary* for this indication, although subject to review following publication of NICE TA299.

Clotrimazole 500mg pessary plus 2% cream (10g) (*Canesten Combi Pack*)	For the treatment of candidal vaginitis and vulvitis.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Dapoxetine 30mg and 60mg tablets (*Priligy*)	For the treatment of premature ejaculation in men aged 18 to 64 years.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*
Ethinylestradiol 30 microgram /levonorgestrel 150 microgram tablets (*Levest/Rigevidon*)	For oral contraception	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*
Ethinylestradiol 30 microgram /levonorgestrel 150 microgram tablets (*Microgynon 30*/ *Ovranette*)	For oral contraception	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*. New initiations are not recommended.
Felodipine modified release tablets 2.5mg, 5mg and 10mg (generic)	For the treatment of hypertension and the prophylaxis of angina	GREEN Second line option in hypertension subject to NICE guidance. Included in the *Lincolnshire Joint Formulary.*
Lercanidipine 10mg and 20mg tablets (generic)	For the treatment of mild to moderate hypertension.	GREEN First line option in hypertension subject to NICE guidance. Approved for inclusion in the *Lincolnshire Joint Formulary*
Macrogol (polyethylene glycol) 3350 oral powder 13.125g plus electrolytes (*Laxido Orange*)	For chronic constipation and faecal impaction	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*
Macrogol (polyethylene glycol) 3350 oral powder 13.125g plus electrolytes (*Molaxole*)	For chronic constipation and faecal impaction	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*
Macrogol (polyethylene glycol) 3350 oral powder 13.125g plus electrolytes (*Movicol*)	For chronic constipation and faecal impaction	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*
Methylprednisolone acetate injection 40mg/ml (*Depo-Medrone*)	For corticosteroid responsive conditions such as severe allergic rhinitis, asthma, rheumatoid arthritis, osteoarthritis, SLE, Stevens-Johnson syndrome, ulcerative colitis, Crohn's disease	GREEN Included in *the Lincolnshire Joint Formulary.*
Methylprednisolone acetate 40mg/lidocaine 10mg/ml injection (*Depo-Medrone with Lidocaine*)	For local use in inflammatory or rheumatic conditions	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*
Morphine sulphate modified release tablets 10mg, 30mg, 60mg and 100mg (*Filnarine SR*)	For severe chronic pain and/or pain resistant to other analgesics, in particular pain associated with cancer.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* as an alternative to *Morphgesic* or *Zomorph.*
Nicotine 2.5mg orodispersible film (*NiQuitin Strips Mint*)	To aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*
Nicotine 1mg per dose oromucosal spray (*Nicorette QuickMist*)	To aid smokers wishing to quit or reduce prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*
Peginterferon alfa 2a injection (*Pegasys*)	For use in combination with ribavirin for the treatment of chronic hepatitis C in children and adolescents 5 years of age and older who test positive for serum hepatitis C virus(HCV) ribonucleic acid (RNA) and who have not previously received any treatment.	RED Approved for inclusion in the *Lincolnshire Joint Formulary*; already approved for use in adult patients for this indication.
Peginterferon alfa-2b injection (*ViraferonPeg*)	For use in combination with ribavirin for the treatment of chronic hepatitis C in children and adolescents 3 years of age and older with CHC without hepatic decompensation who	RED Approved for inclusion in the *Lincolnshire Joint Formulary*; already approved for use in adult patients for this indication.

	test positive for serum hepatitis C virus (HCV) ribonucleic acid (RNA) and who have not previously received any treatment.	
Ranibizumab intravitreal injection (*Lucentis*)	For the treatment of visual impairment due to choroidal neovascularisation secondary to pathologic myopia.	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. Other indications are already approved by NICE and included in the *Formulary*.
Timolol 0.25% eye drops (generic) (5ml bottle)	Ocular hypertension (OHT), chronic open angle glaucoma (COAG) and secondary glaucoma	AMBER without shared care. First line beta-blocker (BB) eye preparation of choice. Included in the *Lincolnshire Joint Formulary*.
Timolol 0.5% eye drops (generic) (5ml bottle)	OHT, COAG and secondary glaucoma	AMBER without shared care. First line BB eye preparation of choice. Included in the *Lincolnshire Joint Formulary*.
Timolol 0.25% and 0.5% solution in preservative free unit dose vials (*Timoptol*) (30 x 0.2ml)	OHT, COAG and secondary glaucoma	AMBER without shared care. Preservative free preparations should only be used in genuine cases of hypersensitivity to the preservative or following corneal transplant surgery. Included in the *Lincolnshire Joint Formulary*.
Timolol 0.25% and 0.5% gel forming eye drops (*Timoptol LA*) (2.5ml)	OHT and COAG and secondary glaucoma	AMBER without shared care. Once daily timolol eye preparation of choice. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Timolol 0.1% preservative free single dose ophthalmic gel (*Tiopex*)	OHT and COAG	AMBER without shared care. Once daily preservative free timolol eye preparation of choice. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Varicella zoster virus vaccine (*Zostavax*)	For the prevention of shingles and Post Herpetic Neuralgia (PHN) in adults > 50.	A national vaccination programme has now made varicella virus vaccine available on the NHS to those aged 70 or 79 (the first wave of a programme designed to eventually offer vaccination to those aged between 70 and 79). Varicella zoster virus vaccine (Zostavax) should not be prescribed outside of this age range on NHS prescription and is designated RED-RED.

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS in Lincolnshire website (www.lincolnshire.nhs.uk); follow the commissioning link to PACEF. Electronic copies of both the *PACE Bulletin* and our sister publication *PACE Shorts* (a short summary of the *PACE Bulletin*) are circulated to a wide readership via email. If you are not currently on our distribution list and wish to receive regular copies of PACEF publications please contact Sandra France on sandra.france@gemcsu.nhs.uk.

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

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NEW DRUG ASSESSMENT: *DAPOXETINE 30MG AND 60MG TABLETS (PRILIGY)*

PACEF have evaluated dapoxetine 30mg and 60mg tablets (*Priligy*) within the context of available evidence and in comparison with a range of unlicensed alternatives and have concluded that prescribing of any treatment for premature ejaculation on the NHS cannot be justified in an environment in which competing health needs of much greater urgency need to be prioritised. As a result of this, dapoxetine 30mg and 60mg tablets (*Priligy*) are designated RED-RED and should not be prescribed. Alternative unlicensed therapies such as selective serotonin reuptake inhibitors (SSRIs) should not be initiated in new patients for this indication; existing patients can continue to receive prescriptions until they or their clinician consider it appropriate to stop.

Serotonin is known to have an inhibitory effect on ejaculation and antidepressants that increase serotonin levels, such as selective serotonin reuptake inhibitors (SSRIs), can be associated with delayed ejaculation as an adverse effect. Capitalizing on this, SSRI antidepressants such as paroxetine, sertraline and fluoxetine have been used off-label to treat premature ejaculation. Dapoxetine (*Priligy*) is the first SSRI to receive a marketing authorization in the UK for this indication. It is highly potent, achieving maximum serum concentrations within 1 to 2 hours; it also has a short half-life (1.5 hours) that ensures rapid elimination post-dose and allows for on demand dosing in contrast to the long-term regular daily dosing required with alternative SSRIs.

The efficacy and safety of dapoxetine have been established in 5 randomised double blind placebo controlled trials. In these studies, the intravaginal ejaculatory latency time (IELT) was increased in the dapoxetine group from a baseline mean of 0.9 minutes to 3.5 to 4.2 minutes. An increase in IELT of at least 1 minute was perceived as clinically meaningful by the men taking part in the trials; in two of these trials placebo alone achieved clinically meaningful results based on this definition, with a quarter of all men taking the placebo reporting some positive effect on their condition. Patient reported outcomes from these studies were positive with increased satisfaction from sexual intercourse and reduction in personal distress and interpersonal difficulties associated with premature ejaculation. The main adverse effects reported were nausea, dizziness and headache. Dapoxetine appears to have no effect on mood and has not been linked with treatment emergent anxiety or suicidality. Between 28 and 38% of men in the trials discontinued treatment due to lack of response. At present, there are no studies comparing dapoxetine with any other active treatment or alternative treatment approaches such as behavioural therapy or psychotherapy; in addition there has been no evaluation of safety and efficacy beyond 24 weeks. Having said this, on demand dosing of dapoxetine is likely to be better tolerated than the regular daily long-term use of alternative unlicensed SSRIs such as paroxetine, fluoxetine, sertraline or escitalopram.

Dapoxetine (*Priligy*) is indicated for the treatment of premature ejaculation in men aged 18 to 64 years. The recommended starting dose of 30mg is taken as needed approximately 1 to 3 hours before anticipated sexual activity; a 60mg strength is also available for those insufficiently responsive to the 30mg dose who experience no adverse reactions to the lower strength. The Summary of Product Characteristics (SPC) specifies that *Priligy* should only be prescribed in men who have:

(1) An IELT of less than 2 minutes AND
(2) Persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the patient wishes AND
(3) Marked personal distress or interpersonal difficulty as a consequence of premature ejaculation AND
(4) Poor control over ejaculation AND

(5) A history of premature ejaculation in the majority of intercourse attempts over the prior 6 months.

While these criteria for initiation appear to be restrictive, PACEF are concerned that the majority of presenting patients could be deemed to meet them based on poorly defined terminology, patient pressure and subjective clinical assessment. A recent review of the product by the Midlands Therapeutic Review and Advisory Committee (MTRAC) concluded that effective patient diagnosis and assessment utilizing these criteria could only be undertaken through a specialist service such as a psychosexual clinic. Such a service could also undertake an individual benefit and risk assessment after 4 weeks of therapy and clinically re-assess every six months. In the absence of widely available psychosexual services in Lincolnshire, issues remain around effective diagnosis, assessment and review.

What are the alternatives?

Dapoxetine (*Priligy*) is the first licensed treatment for the management of premature ejaculation and has been available in some European countries for some time. However, unlicensed alternative treatments are also available including:

- Other SSRIs, such as escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline. These agents need to be taken regularly each day with potential improvement seen within days of initiation and maximum effect within four weeks. Any patients in Lincolnshire currently receiving treatment for premature ejaculation are likely to be taking a long-term regular unlicensed SSRI.
- Clomipramine: a tricyclic antidepressant with evidence of efficacy for both continuous and on demand doses. Both patients and partners report improved sexual satisfaction, but use is limited by adverse effects.
- Desensitizing agents such as lidocaine 2.5%/prilocaine 2.5% cream (*EMLA Cream*), *SS Cream* (a herbal preparation) and lidocaine/prilocaine spray formulations such as *Tempe* spray. Local anaesthetic based products desensitise the penis and are usually applied about 20 minutes prior to intercourse. There is RCT evidence to support their use, but they should be used with a condom to reduce the risk of impaired vaginal sensation and local irritation.
- PDE5 inhibitors (e.g. sildenafil, vardenafil and tadalafil). There is minimal evidence to support the use of any of the PDE5 inhibitors. Epidemiological studies have shown that about a third of men diagnosed with erectile dysfunction also suffer from premature ejaculation. Sufferers from erectile dysfunction may resort to over-stimulation to achieve a rigid erection which in turn leads to premature ejaculation. In such patients, treatment of erectile dysfunction with a PDE5 inhibitor may also improve premature ejaculation.
- Centrally acting opioid analgesics. There is evidence from one published trial and some case reports that support the use of tramadol. Reports of premature ejaculation in men withdrawing from opiate addiction suggest a possible relationship between central opioid receptors and ejaculatory control.

How do these alternatives compare to dapoxetine?

The table below summarizes comparative information about each of the major alternative therapies including dapoxetine and is adapted from a review article entitled 'Medical therapy for premature ejaculation' by Amar Mohee and Ian Eardley that first appeared in *Therapeutic Advances in Urology* in September 2011:

Drug	Dose	Frequency	Relative increase in intravaginal ejaculation latency time	Adverse effects

			(IELT)	
Antidepressants – unlicensed use				
clomipramine	12.5-50mg	Prn or daily dose	4	Fatigue, nausea, dizziness, dry mouth , hypotension
escitalopram	20-40mg	Daily dose	2	Fatigue, nausea, diarrhoea, yawning, diaphoresis, erectile dysfunction, decreased libido, perspiration. Increased suicide risk
fluoxetine	20-40mg		5	
fluvoxamine	25-50mg		1.5	
paroxetine	10-40mg		8	
sertraline	50-200mg		5	
Licensed therapy				
dapoxetine	30-60mg	prn	2.5 - 3.0	Nausea, diarrhoea, headache, dizziness
Desensitizing agents				
EMLA cream	smear	prn	4-8	Messy, numbing of vagina, skin irritation, erectile dysfunction
SS cream	smear			
TEMPE (PSD502)	spray			
PDE5 inhibitors				
vardenafil	10mg	prn	3	Headache, flushing, nausea.
Centrally acting opioid analgesic				
tramadol	50mg	prn	3.6 - 7.0	Dizziness, drowsiness, nausea, constipation

From this, we can conclude that dapoxetine is not as effective as many alternative unlicensed treatments, but may be more convenient and better tolerated.

A cost comparison against alternative unlicensed SSRIs reveals that dapoxetine is significantly more expensive than alternative unlicensed longer acting SSRIs.

Drug	Daily dose	Cost (£) (doses)
Dapoxetine 30mg and 60mg tablets (*Priligy*)	30-60mg	30mg £14.71 (3) 30mg £26.48 (6) 60mg £19.12 (3) 60mg £34.42 (6)
Fluoxetine 20mg capsules	20-40mg	20mg £1.10 (30) 20mg x 2 £2.20 (30)
Paroxetine 10mg, 20mg and 30mg tablets	10-40mg	10mg £12.89 (28) 20mg £1.60 (30) 30mg £2.17 (30) 2 x 20mg £3.20 (30)
Sertraline 50mg and 100mg tablets	50 – 200mg	50mg £3.26 (28) 100mg £5.78 (28)

Treatment costs with dapoxetine assume average use of 3 to 6 times a month; in the trials most patients were using at least 6 doses a month; equivalent costs for fluoxetine, paroxetine and sertraline assume continuous daily administration. MTRAC have estimated that the annual cost of maintaining one patient on dapoxetine is between £344 and £448.

PACEF Recommendation:

From randomized controlled trials, dapoxetine (*Priligy*) emerges as superior to placebo in the treatment of premature ejaculation, extending IELT from a baseline mean of 0.9 minutes to 3.5 to 4.2 minutes. When used on demand, it seems to be effective in many, is convenient and well tolerated. However, there is no comparative data against alternative therapies and no long-term safety data. Comparison of increase in IELT with a range of alternatives reveals that dapoxetine may be less effective than many other treatment options. A cost comparison illustrates that dapoxetine on demand is significantly more expensive than alternative unlicensed

treatment options. While the criteria for initiation specified in the product SPC appear to be restrictive, PACEF are concerned that the majority of presenting patients could be deemed to meet them based on poorly defined terminology, patient pressure and subjective clinical assessment. The need for specialist diagnosis, assessment and review requires locally accessible psychosexual services. In the absence of such services, PACEF have concluded that dapoxetine 30mg and 60mg tablets (*Priligy*) should be designated RED-RED and should not be prescribed. Similarly, prescribing of any treatment for premature ejaculation on the NHS cannot be justified in an environment in which competing healthcare needs of much greater urgency must be prioritised. As a result of this, alternative unlicensed therapies such as selective serotonin reuptake inhibitors (SSRIs) should not be initiated in new patients for this indication; existing patients can continue to receive prescriptions until they or their clinician consider it appropriate to stop. This decision will be kept under review.

References

London New Drugs Group/London Medicines Evaluation Network Review, *Dapoxetine (Priligy) for premature ejaculation* (November 2013).
Amar Mohee and Ian Eardley, Medical therapy for premature ejaculation, *Therapeutic Advances in Urology* (September 2011).
Midlands Therapeutic Review and Advisory Committee, Commissioning Support: *Dapoxetine (Priligy) for the treatment of premature ejaculation* (November 2013).

NEW FORMULATION ASSESSMENT: *NICOTINE 2.5MG ORODISPERSIBLE FILM (NIQUITIN STRIPS MINT)*

PACEF were disappointed by the limited trial evidence reviewed as part of this assessment and have not approved nicotine 2.5mg orodispersible film (*NiQuitin Strips Mint*) for use as an aid to smoking cessation.

Nicotine 2.5mg orodispersible film (*NiQuitin Strips Mint*) is a rapid acting oral nicotine formulation launched by GlaxoSmithKline as an addition to the established *NiQuitin* range that includes transdermal patches, chewing gum and lozenges. The orodispersible film is placed on the tongue and pushed onto the roof of the mouth where it takes approximately 3 minutes to completely dissolve.

Nicotine Replacement Therapy (NRT) is already well recognized as first line pharmacotherapy designed to support patients experiencing craving or nicotine withdrawal symptoms linked to an attempt to reduce or stop smoking. Nicotine 2.5mg orodispersible film (*NiQuitin Strips Mint*) has a marketing authorisation: (1) to aid smokers wishing to quit or reduce prior to quitting and (2) to assist smokers who are unwilling or unable to smoke (e.g. due to an inpatient hospital stay). *NiQuitin Strips Mint* are licensed for use in adolescents aged 12 to 17 and adults, including pregnant and breast-feeding women.

PACEF reviewed a single randomized open label parallel group study in 322 patients comparing *NiQuitin Strips* with 2mg nicotine lozenges with a primary outcome of effect on breakthrough cravings. Patients abstained from smoking and were then asked to light their preferred brand of cigarette and hold it for a minute, without placing it in their mouth, to produce a cue-provoked breakthrough craving. *NiQuitin Strips* were found to be significantly more effective than 2mg lozenges at relieving cue-provoked cravings at 50 seconds, 3 and 5 minutes. In the absence of comparative data against anything other than nicotine lozenges, PACEF were unable to form a judgement as to whether *NiQuitin Strips* provided a cost-effective alternative to other rapid acting nicotine formulations, such as nicotine oromucosal spray (*Nicorette QuickMist*).

NICE Public Health Guidance (PH10) on smoking cessation services (February 2008) makes no specific recommendations as to which type of pharmacotherapy is preferred (i.e. NRT, varenicline or bupropion). Choice is dependent on a number of factors including

likely compliance, availability of counselling, previous use of cessation therapies, contraindications, adverse effects, and patient preference. NICE also recognise a need for combination NRT including nicotine patches plus gum, lozenge, inhalator or nasal spray depending on the degree of nicotine dependence or previous failed attempt to quit using monotherapy. Nicotine containing patches are used to control background cravings, with an intermittent format recommended for use on an as needed basis when breakthrough cravings arise. Increasingly NRT is being used to help people to reduce in preparation to quit as well as to support outright quit attempts.

Cost comparison of different forms of NRT is difficult as daily dose within a recommended range is dependent on the needs of the individual and combination therapy is increasingly common. Nonetheless, *NiQuitin Strips* emerge as higher in cost than standard lozenges and chewing gums and more competitively priced with premium price formulations such as *Nicorette QuickMist, Nicorette Nasal Spray* and *Nicorette Inhalator*.

PACEF Recommendation:
The single study reviewed as part of this assessment did not provide sufficient evidence to support the inclusion of nicotine 2.5mg orodispersible film (*NiQuitin Strips Mint*) in the *Lincolnshire Joint Formulary*. As a result of this, nicotine 2.5mg orodispersible film (*NiQuitin Strips Mint*) are designated RED-RED and should not be prescribed, even if requested by local specialist smoking cessation services. Where a rapid acting nicotine formulation is indicated, nicotine 1mg per dose oromucosal spray (*Nicorette QuickMist*) has been evaluated by PACEF and designated GREEN (see *PACE Bulletin*, Vol 5 No 9 (May 2011)). A wider review of smoking cessation therapies is in progress and will be published later in the year.

RAPID DRUG ASSESSMENTS: *TIMOLOL 0.1% SINGLE DOSE PRESERVATIVE FREE EYE GEL (TIOPEX) AND TIMOLOL 0.25% AND 0.5% OPHTHALMIC GEL FORMING SOLUTION (TIMOPTOL LA)*

Timolol 0.25% and 0.5% eye drops are used for the treatment of ocular hypertension and chronic open angle glaucoma and both strengths are approved for use on the *Lincolnshire Joint Formulary*. Historically, timolol 0.1% eye gel (*Nyogel*) was also approved for use as a once daily gel formulation. Following the withdrawal of *Nyogel*, PACEF have approved timolol 0.25% and 0.5% ophthalmic gel-forming solution (*Timoptol-LA*) and timolol 0.1% unit dose eye gel (*Tiopex*) (preservative free) as replacement preparations. All of these products are designated AMBER without shared care and approved for use on *Lincolnshire Joint Formulary.*

ORDERING AND CLAIMING FOR VARICELLA ZOSTER VIRUS VACCINE (*ZOSTAVAX*)

As reported in a previous issue (Volume 7, No 20 (December 2013), varicella zoster virus vaccine (*Zostavax*) has now been made available on the NHS through a national vaccination programme for those aged 70 or 79 (the first wave of a programme designed to eventually offer vaccination to those aged between 70 and 79). Vaccine required to support the limited roll-out of the national programme is available free-of-charge and can be ordered online via the ImmForm website (www.immform.dh.gov.uk); the vaccine is distributed by Movianto UK (01234 248631).There is no need to claim from the NHS Business Services Authority Prescription Pricing Division for this vaccine as it has been provided free of charge. Our understanding is that *Zostavax* is currently available from ImmForm, although there is an order restriction of 20 doses per practice per week.

Although *Zostavax* holds an appropriate marketing authorisation for a wider age range of patients encompassing those aged 50 to 69, PACEF do not recommend prescribing of

Zostavax for this group and the product remains RED-RED both for this age range and for those between 70 and 79 (where the national programme covers vaccine supply).

Vaccines for private prescriptions, outbreaks, occupational health use or travel are NOT provided free of charge and should be ordered from Sanofi Pasteur MSD direct on 0800 0855511. Any vaccine supplied and administered outside of the national programme can be claimed for where applicable from the NHSBSA PPD in the usual way, although the RED-RED status of the product in county severely limits use outside the national programme. Where a claim is made to the NHSBSA PPD, individual FP10 prescriptions should be used as this is not covered by the monthly claim form.

PACEF Recommendation:
All *Zostavax* vaccine required for the national vaccination programme can be ordered free of charge from ImmForm. Individual FP10 prescriptions should not be submitted to the NHSBSA PPD as claims for reimbursement. Practices that have inadvertently over-claimed for *Zostavax* from the PPD can rectify the claim by emailing the NHS BSA on nhsbsa.prescriptionservices@nhs.net giving details of what they have claimed, when they submitted the claim and what they wish to rectify. Prescription Services will then make any necessary changes to their reimbursement.

Reference
Joint Committee on Vaccination and Immunisation, *Immunisation Against Infectious Disease*, Chapter 28a Shingles (herpes zoster)

LINCOLNSHIRE JOINT FORMULARY UPDATE

BNF 1.6.4 *Osmotic laxatives*

Laxido Orange and *Molaxole* are equivalent macrogol (polyethylene glycol) osmotic laxative formulations and are significantly lower in cost than *Movicol*. As a result of this, both *Laxido Orange* and *Molaxole* are designated GREEN and approved for inclusion on the *Joint Formulary.* Standard *Movicol* is not approved for use, although it is recognized that lower dose *Movicol* preparations, *Movicol-Half* and *Movicol Paediatric Plain* retain a role.

BNF 2.5.5 *Drugs affecting the renin angiotensin system*

Both ramipril capsules and ramipril tablets (generic; all strengths) are approved for use on the *Joint Formulary*.

BNF 2.6.2 *Calcium channel blockers*

Generic amlodipine 5mg and 10mg tablets and lercanidipine 10mg and 20mg tablets are now available as low cost generics. Both drugs are approved for inclusion in the *Joint Formulary* as potential first line choices for the treatment of hypertension subject to NICE guidance and are designated GREEN. Felodipine modified release tablets 2.5mg, 5mg and 10mg are also included in the *Joint Formulary*, but are recommended second line on the grounds of cost (see cost comparison).

Drug	Dose	Cost
Amlodipine 5mg tablets	5mg once daily	£0.97 (28)
Amlodipine 10mg tablets	10mg once daily	£1.04 (28)
Lercanidipine 10mg tablets	10mg once daily	£1.48 (28)
Lercanidipine 20mg tablets	20mg once daily	£1.74 (28)
Felodipine modified release tablets 2.5mg	2.5mg daily in the morning	£6.31 (28)
Felodipine modified release tablets 5mg	5mg daily in the morning	£4.21 (28)

Felodipine modified release tablets 10mg	10mg daily in the morning	£5.66 (28)

BNF 4.7.2 *Opioid analgesics*

Filnarine SR is a new modified release morphine preparation even lower in cost than *Morphgesic* and *Zomorph*. It is available in 10mg, 30mg, 60mg and 100mg strengths and is approved for inclusion in the *Joint Formulary*. Designation: GREEN.

BNF 7.2.2 *Vaginal and vulval infections*

The *Canesten Combi Pack* (containing clotrimazole 500mg pessary plus 2% cream (10g) has been approved for inclusion in the *Joint Formulary* on the basis that the individual components prescribed separately are more costly (see cost comparison):

Products	**Cost**
Clotrimazole 500mg vaginal pessary (generic)	£2.00 (1)
Clotrimazole 2% cream (*Canesten Thrush Cream*)	£4.46 (20g)
Clotrimazole 500mg pessary plus 2% cream (10g)(*Canesten Combi Pack*)	£5.21 (pack)

BNF 7.3.1 *Combined hormonal contraceptives*

There are now four ethinylestradiol 30 microgram /levonorgestrel 150 microgram combined oral contraceptive tablet formulations available in the UK: *Levest*, *Microgynon 30*, *Ovranette* and *Rigevidon*. Of these, *Levest* and *Rigevidon* are lower cost and designated GREEN; both products are approved for inclusion in the *Joint Formulary*. In comparison, *Microgynon 30 and Ovranette* are more expensive and should no longer be initiated in new patients; *Microgynon 30 and Ovranette* are designated RED-RED and have been removed from the *Joint Formulary.*

Products	**Cost of 3 x 21**
Levest	£1.80
Microgynon 30	£2.82
Ovranette	£2.20
Rigevidon	£1.89

BNF 10.1.2.2 *Local corticosteroid injections*

Methylprednisolone acetate 40mg/lidocaine 10mg/ml injection (*Depo-Medrone with Lidocaine*) is approved for inclusion in the *Joint Formulary;* designation GREEN. *Depo-Medrone* injection is already included in the *Formulary* and *Depo-Medrone with Lidocaine* is only marginally more expensive than the separate components.

IMMEDIATE RELEASE TWICE DAILY QUETIAPINE TABLETS NOW PREFERRED TO MODIFIED RELEASE FORMULATIONS

PACEF are in support of the review of all patients currently taking modified release quetiapine tablets (either generic or brand, such as *Seroquel XL*) with the object of moving as many people as possible to an equivalent dose of immediate release quetiapine tablets.

Since the patent expiry of quetiapine in 2012 and the launch of generic tablet formulations, the *Drug Tariff* reimbursement price for immediate release quetiapine tablets has fallen significantly. The cost comparison below illustrates the extent to which the price of

immediate release tablets has fallen below modified release equivalent products such as *Seroquel XL*.

	Dose	Cost (30 days treatment)
Quetiapine 25mg tablets (generic)	25mg twice daily	£1.61
Quetiapine 50mg MR tablets (*Seroquel XL*)	50mg once daily	£33.83
Quetiapine 100mg tablets (generic)	100mg twice daily	£2.66
Quetiapine 200mg MR tablets (*Seroquel XL*)	200mg once daily	£56.55
Quetiapine 150mg tablets (generic)	150mg twice daily	£3.27
Quetiapine 300mg MR tablets (*Seroquel XL*)	300mg once daily	£85.00
Quetiapine 200mg tablets (generic)	200mg twice daily	£3.72
Quetiapine 400mg MR tablets (*Seroquel XL*)	400mg once daily	£113.10
Quetiapine 300mg tablets (generic)	300mg twice daily	£5.07
Quetiapine 400mg MR plus quetiapine 200mg MR tablets (*Seroquel XL*)	400mg plus 200mg once daily	£169.65

Quetiapine is licensed for the treatment and prevention of relapse in schizophrenia and the treatment and prevention of mania and depression in bipolar disorder. There are minimal differences between immediate release and modified release formulations of quetiapine. The maximum plasma concentration and total amount of drug absorbed is comparable for a daily dose of MR quetiapine and the same total daily dose given twice daily of immediate release quetiapine (i.e. 100mg twice daily from an immediate release formulation is directly equivalent to 200mg given as a single daily MR dose). The only difference is that the more rapid absorption of the active drug from the immediate release formulation could result in a higher incidence of sedation from the immediate release tablet than the modified release. A published study from 2008 evaluated a switch from modified release quetiapine to immediate release quetiapine tablets and found no significant changes in efficacy, safety or tolerability between the two formulations.

PACEF Recommendation:

In view of the significant cost difference between immediate release quetiapine tablets and modified release quetiapine and the comparable efficacy and safety of the two formulations, clinicians are urged to review all patients currently prescribed quetiapine modified release formulations (either generic or brand) with a view to changing their therapy to an equivalent dose of immediate release quetiapine tablets. The total daily dose can usually be split to be taken twice daily as an immediate release quetiapine tablet formulation; immediate release quetiapine and MR quetiapine products can be assumed to be equivalent mg for mg. For the treatment of depression in bipolar disorder, standard quetiapine is usually given once daily.

Reference:

Trent Medicines Information Service, *QIPP Detail Aid: Quetiapine – Use Plain Tablets* (October 2013)

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 298: *RANIBIZUMAB FOR TREATING CHOROIDAL NEOVASCULARISATION ASSOCIATED WITH PATHOLOGICAL MYOPIA* (NOVEMBER 2013)

Ranibizumab is recommended as an option for treating visual impairment due to choroidal neovascularisation secondary to pathological myopia when the manufacturer provides ranibizumab with the discount agreed in the patient access scheme.

PACEF Recommendation:
Ranibizumab intravitreal injection (*Lucentis*) is designated RED for this indication. Ranibizumab (*Lucentis*) is already approved by NICE for the treatment of age related macular degeneration, visual impairment due to diabetic macular oedema and the treatment of visual impairment caused by macular oedema secondary to retinal vein occlusion. Ranibizumab (*Lucentis*) is approved for inclusion in the *Joint Formulary* for this indication.

NICE TECHNOLOGY APPRAISAL 299: *BOSUTINIB FOR PREVIOUSLY TREATED CHRONIC MYELOID LEUKAEMIA* (NOVEMBER 2013)

Bosutinib is not recommended within its marketing authorisation for treating Philadelphia-chromosome-positive chronic myeloid leukaemia (CML). People currently receiving bosutinib for this indication should be able to continue treatment until they and their clinician consider it appropriate to stop.

PACEF Recommendation:
Through the *National Cancer Drugs Fund List*, bosutinib is approved for the treatment of chronic, accelerated or blast phase Philadelphia chromosome positive chronic myeloid leukaemia (CML) previously treated with one or more tyrosine kinase inhibitors and where imatinib, nilotinib and dasatinib are not appropriate. The drug has been previously designated as RED by PACEF in response to the *NCDL*. PACEF have previously established that a drug can still be considered and approved by the *NCDL* despite a negative NICE TA. There is a possibility that bosutinib may remain on the *NCDL* in spite of NICE TA 299, although this is subject to review. As long as the drug remains on the *NCDL* it will continue to be designated RED and remain available through the *Joint Formulary*. As a result of this, bosutinib 100mg and 500mg tablets (*Bosulif*) will continue to be designated RED for this indication.

NICE TECHNOLOGY APPRAISAL TA300: *PEGINTERFERON ALFA AND RIBAVIRIN FOR TREATING CHRONIC HEPATITIS C IN CHILDREN AND YOUNG PEOPLE* (NOVEMBER 2013)

Peginterferon alfa in combination with ribavirin is recommended, within its marketing authorisation, as an option for treating chronic hepatitis C in children and young people. NICE TA200 already recommends combination therapy with peginterferon alfa (2a or 2b) and ribavirin as a treatment option for adults with chronic hepatitis C (CHC).

PACEF Recommendation:
Peginterferon alfa-2a (*Pegasys*) in combination with ribavirin has a UK marketing authorisation for the treatment of children and adolescents 5 years of age and older with CHC who test positive for serum hepatitis C virus(HCV) ribonucleic acid (RNA) and who have not previously received any treatment. Peginterferon alfa-2b

(*ViraferonPeg*) in combination with ribavirin has a UK marketing authorisation for the treatment of children and adolescents 3 years of age and older with CHC without hepatic decompensation who test positive for serum hepatitis C virus (HCV) ribonucleic acid (RNA) and who have not previously received any treatment. Both peginterferon alfa 2a injection (*Pegasys*) and peginterferon alfa 2b injection (*ViraferonPeg*) are approved for use in combination with ribavirin for the treatment of chronic hepatitis C in children and young people subject to marketing authorisation. Designation: RED; approved for inclusion in the *Joint Formulary* for this patient group.

Postscript: *Aripiprazole (Abilify) for the treatment of schizophrenia and the treatment and prevention of mania*

Following our recent coverage of the use of aripiprazole (*Abilify*) for the treatment of moderate to severe manic episodes in adolescents with bipolar disorder, LPFT have asked us to clarify that aripiprazole is designated RED for this indication, but continues to be designated AMBER without shared care for the treatment of schizophrenia and the treatment and prevention of mania.

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