NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 7; Number 5 **March 2013**

What's new this month?

- **Temazepam 10mg and 20mg tablets are in short supply with reimbursement prices soaring to levels almost 10 times higher than the pre-crisis *Tariff* rates. With no prospect of this problem resolving in the short-term, prescribers are urged to take this opportunity to reduce or stop hypnotic use wherever possible. All patients currently taking temazepam 10mg or 20mg tablets should be prioritised for review and options explored to reduce or stop temazepam use or switch to an alternative low cost z drug such as generic zopiclone. Continued prescribing of temazepam 10mg and 20mg tablets is likely to be extremely costly in the coming months but may still be necessary for some people (see page 3).**
- **Current supply problems with isosorbide mononitrate standard release 10mg, 20mg and 40mg tablets are driving switches to isosorbide mononitrate modified release formulations (as recommended by the Department of Health). Prescribers should ensure that all ISMN MR prescribing is by low cost brand in order to minimize the financial impact of this shortage in supply (see page 5).**
- **Saxagliptin/metformin tablets (*Komboglyze*) for the treatment of type 2 diabetes mellitus have been designated GREEN (see page 6).**
- **Glycopyrronium bromide inhaler (*Seebri Breezhaler*), a new long acting muscarinic antagonist (LAMA) for the maintenance treatment of chronic obstructive pulmonary disease (COPD), has been designated GREEN (see page 8).**
- **Recent studies have confirmed the limited effectiveness of Z drugs in the treatment of adult insomnia and suggested a possible association between hypnotic use and dementia (see page 10).**
- **Concurrent use of non-steroidal anti-inflammatory drugs with diuretics and either ACE inhibitors or Angiotensin Receptor Blockers can increase the risk of acute kidney injury by as much as 31%; the highest risk is in the first 30 days of concurrent therapy (see page 10).**
- **NICE have approved rivaroxaban (*Xarelto*) for the treatment of deep vein thrombosis and prevention of recurrent deep vein thrombosis and pulmonary embolism. Designation RED pending the development of further guidance (see page 11).**
- **NICE have approved mannitol dry powder for inhalation (*Bronchitol*) for the treatment of cystic fibrosis in adults who cannot use dornase alfa and whose lung function is rapidly declining and for whom other osmotic agents are not considered appropriate. It is designated RED at this stage with the prospect for future consideration of AMBER (with shared care) in consultation with specialist services (see page 13).**
- **NICE have approved ivabradine (*Procoralan*) for the treatment of stable chronic heart failure within license. This consolidates pre-existing PACEF advice: ivabradine (*Procoralan*) is designated AMBER without shared care for this indication (see page 13).**

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SUMMARY OF PACEF DECISIONS: *JANUARY/FEBRUARY 2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Alteplase injection (*Actilyse*)	For the treatment of acute ischaemic stroke	RED Already on the Joint Formulary
Decitabine infusion (*Dacogen*)	For newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in patients unsuitable for standard induction chemotherapy.	RED-RED Not approved for Joint Formulary.
Denosumab injection (*XGEVA*) 120mg	For the prevention of skeletal-related events in adults with bone metastases from breast cancer and from solid tumours.	RED Further guidance is in development which may result in a revised classification. Approved for Joint Formulary for this indication.
Denosumab injection (*XGEVA*) 120mg	For the prevention of skeletal-related events in adults with bone metastases from prostate cancer.	RED-RED Not approved for Joint Formulary for this indication.
Glycopyrronium bromide inhaler (*Seebri Breezhaler*)	For the maintenance treatment of COPD	GREEN Second line alternative to tiotropium bromide (*Spiriva HandiHaler*) Approved for Joint Formulary
Ipilimumab infusion (*Yervoy*)	For the treatment of advanced unresectable or metastatic melanoma, following prior therapy.	RED Approved for Joint Formulary
Ivabradine tablets 5mg and 7.5mg (*Procoralan*)	For the treatment of stable chronic heart failure (CHF) (NYHA class II to IV) with systolic dysfunction in patients in sinus rhythm with heart rate ≥75 beats per minute (bpm) in combination with standard therapy including a beta-blocker (BB) or when BBs are contra-indicated or	AMBER without shared care. Already on the Joint Formulary for this indication; also approved for use within license for chronic stable angina. .

	not tolerated.	
Mannitol dry powder for inhalation (*Bronchitol*)	For the treatment for cystic fibrosis (CF) in adults (aged 18 years and above) as an add-on therapy to best standard of care.	RED Shared care arrangements may be developed at a later date. Approved for Joint Formulary.
Rivaroxaban (*Xarelto*) 15mg and 20mg film coated tablets	Licensed for the treatment of deep vein thrombosis (DVT) and pulmonary embolus (PE) and for the prevention of recurrent DVT and PE in adults.	AMBER without shared care. Further guidance is in development which may result in a revised classification. Approved for Joint Formulary for this indication.
Saxagliptin/metformin tablets 2.5mg/850mg and 2.5mg/1000mg tablets (*Komboglyze*)	For the management of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximum tolerated dose of metformin alone or those already being treated with a combination of saxagliptin and metformin. Also indicated in combination with insulin as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin and metformin alone do not provide adequate control.	GREEN Approved for Joint Formulary.
Vemurafenib tablets 240mg (*Zelboraf*)	For BRAF V600 mutation-positive unresectable or metastatic melanoma.	RED Approved for Joint Formulary, subject to discount agreed in the patient access scheme.
Zonisamide capsules 25mg, 50mg and 100mg (*Zonegran*)	Monotherapy for partial seizures with or without secondary generalisation in newly diagnosed epilepsy. Adjunctive therapy for partial seizures with or without secondary generalisation.	AMBER No shared care guideline required. Direct specialist supervision of the 5 to 10 week titration period is required. Approved for 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 Lincolnshire website (www.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

MANAGING THE TEMAZEPAM 10MG AND 20MG TABLET SUPPLY PROBLEM

A shortage of temazepam tablets, both 10mg and 20mg strengths, is driving an alarming escalation in the NHS reimbursement price for these medicines. The table below gives an indication of the scale of the price increases since the Autumn of last year:

	September 2012 Reimbursement Price	**February 2013 Reimbursement Price**	**March 2013 Reimbursement Price**
Temazepam 10mg tablets	£2.57 (28)	£24 (28)	£24 (28)
Temazepam 20mg tablets	£2.08 (28)	£25 (28)	£21 (28)

If these prices are sustained, the financial impact on the Lincolnshire Clinical Commissioning Groups (CCGs) is likely to be significant as tabulated below:

	Additional Cost per Quarter (assuming March 2013 prices are sustained for 3 months)	Additional Cost per Year (assuming March 2013 prices are sustained for 12 months)
Lincolnshire East CCG	£68,028	£272,112
Lincolnshire South CCG	£45,402	£181,606
Lincolnshire South West CCG	£25,143	£100,573
Lincolnshire West CCG	£44,170	£176,680
Lincolnshire Total	£182,743	£730,970

What are the best options to manage this?

(1) Take the opportunity to reduce or stop hypnotic use where possible

The current shortage presents an opportunity to review patients taking temazepam long-term. None of the hypnotics currently prescribed in the UK are licensed for long-term use. It is doubtful whether long-term users experience any clinically significant hypnotic effects with continued use; however, there is evidence of psychological dependence in many patients. In addition, use of hypnotics can increase the risk of falling, confusion and cognitive decline, particularly in the elderly.

A recent meta-analysis in the *British Journal of General Practice* found that a brief intervention in the form of either a letter or a single GP consultation with long-term users of benzodiazepines (BZ) was enough to encourage 16 to 30% of patients to decrease or stop their medication[1]. If letters are used, the number needed to post to achieve one additional person discontinuing BZ use is 12. Prescribers considering the option to reduce or stop hypnotic use are referred to *BNF* guidance on withdrawal of benzodiazepines (see section 4.1).

(2) Consider switching temazepam users to generic zopiclone where possible

Three studies have investigated the effect of switching patients from BZ hypnotics to zopiclone with the intention to discontinue hypnotic use altogether[2,3,4]. Within this context, zopiclone has been shown to effectively substitute for BZs, reducing the appearance of 'rebound' and withdrawal effects. Information on equivalent doses of temazepam and zopiclone is sparce, although one review has suggested that zopiclone 7.5mg is at least as effective as 20mg of temazepam[5]. Based on limited evidence suggested dose equivalences are as follows:

	Equivalent zopiclone dose
Temazepam 10mg at night	Zopiclone 3.75mg at night
Temazepam 20mg at night	Zopiclone 7.5mg at night
Temazepam in doses higher than 20mg	Halve the dose of temazepam for several nights and then substitute zopiclone 7.5mg or cross taper.

Note: Zopiclone is cleared more slowly in elderly patients; all patients over 65 should initially receive 3.75mg at night regardless of the dose equivalences documented above.

A cost comparison between the z drugs and temazepam 10mg and 20mg tablets reveals the financial reason for preferring generic zopiclone tablets[6]:

	Dose	Cost of 28 days treatment
Zopiclone 3.75mg tablets	**3.75mg at night**	**£1.52**
Zopiclone 7.5mg tablets	**7.5mg at night**	**£1.43**
Zaleplon 5mg capsules	5mg at night	£3.12
Zaleplon 10mg capsules	10mg at night	£3.76
Zolpidem 5mg tablets	5mg at night	£1.96
Zolpidem 10mg tablets	10mg at night	£1.84
Temazepam 10mg tablets	10mg at night	£24.00
Temazepam 20mg tablets	20mg at night	£21.00

PACEF Recommendations

Take the opportunity to reduce or stop hypnotic use wherever possible. All patients currently taking temazepam 10mg or 20mg tablets should be prioritised for review. As part of the review, explore the options to reduce or stop temazepam use or switch to an alternative low cost z drug such as generic zopiclone using the dose equivalence data documented above. Continued prescribing of temazepam 10mg and 20mg tablets is likely to be extremely costly in the coming months but may still be necessary for some.

References

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5. Wadworth A, McTavish D. *Drugs and Aging* 1993; 3 (5): 441-59
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Acknowledgements

This article is substantially based on work undertaken by the Trent Medicines Information Service that was published as part of the *Rapid Update on Supply Issues* series in February 2013.

MANAGING THE ISOSORBIDE MONONITRATE STANDARD RELEASE 10MG, 20MG AND 40MG TABLET SUPPLY PROBLEM

Due to the temporary closure of the major UK manufacturer of standard release isosorbide mononitrate (ISMN) tablets (Teva), ISMN 10mg, 20mg and 40mg tablets are now in short supply. A recent letter from the Department of Health has advised clinicians to transfer all patients over to an equivalent dose of an ISMN modified release formulation until the problem resolves. Current intelligence suggests that this situation may persist until at least May or June 2013 with the prospect of continuing supply difficulties into the summer.

When transferring patients from standard release ISMN to modified release ISMN the following dose conversion table may be useful:

Standard release dose	Modified release dose
10mg twice daily	30mg daily (usually morning)
20mg twice daily	60mg daily
30mg twice daily	60mg daily
40mg twice daily	90mg daily

As many patients will receive an increased dose as part of standard release to MR conversion, it is unlikely that angina symptoms will worsen; however, the increased dose may increase the incidence of nitrate headache in some.

When switching from standard release ISMN to MR ISMN it is crucial that the MR product is prescribed as a low cost brand. The following cost comparison details the

major brands available and the wide variation in their associated costs. In particular, it illustrates the high reimbursement cost of generically prescribed products. The lowest cost branded product in each of the strength categories is highlighted in bold:

	Cost for 28 tablets/capsules
Isosorbide mononitrate 25mg MR capsules (*Tariff* rate)	£5.13
Isosorbide mononitrate 25mg MR tablets (*Tariff* rate)	£5.95
Isosorbide mononitrate 25mg MR capsules (*Elantan LA*)	**£3.40**
Isosorbide mononitrate 25mg MR capsules (*Isodur 25XL*)	£4.63
Isosorbide mononitrate 25mg MR tablets (*Isotard 25XL*)	£6.75
Isosorbide mononitrate 40mg MR tablets (*Ismo Retard*)	£10.71
Isosorbide mononitrate 40mg MR tablets (*Isotard 40XL*)	£6.75
Isosorbide mononitrate 40mg MR capsules (*Monomax MR*)	**£6.52**
Isosorbide mononitrate 40mg MR tablets (*Zemon 40XL*)	£14.25
Isosorbide mononitrate 50mg MR capsules (*Tariff* rate)	£11.08
Isosorbide mononitrate 50mg MR tablets (*Tariff* rate)	£6.75
Isosorbide mononitrate 50mg MR capsules (*Elantan LA*)	**£3.69**
Isosorbide mononitrate 50mg MR capsules (*Isodur 50XL*)	£6.45
Isosorbide mononitrate 50mg MR tablets (*Isotard 50XL*)	£6.75
Isosorbide mononitrate 60mg MR capsules (*Tariff* rate)	£8.86
Isosorbide mononitrate 60mg MR tablets (*Tariff* rate)	£10.50
Isosorbide mononitrate 60mg MR tablets (*Chemydur 60XL*)	**£3.49**
Isosorbide mononitrate 60mg MR tablets (*Imdur Durules*)	£10.50
Isosorbide mononitrate 60mg MR tablets (*Isib 60XL*)	£8.15
Isosorbide mononitrate 60mg MR tablets (*Isotard 60XL*)	£5.75
Isosorbide mononitrate 60mg MR capsules (*Monomax MR*)	£8.86
Isosorbide mononitrate 60mg MR tablets (*Monomax XL*)	£5.25
Isosorbide mononitrate 60mg MR tablets (*Monomil XL*)	**£3.98**
Isosorbide mononitrate 60mg MR tablets (*Monosorb 60XL*)	£15.35

PACEF Recommendations:

Current supply problems with standard release ISMN tablets 10mg, 20mg and 40mg are driving switches to equivalent dose MR formulations. In order to minimize the financial impact of this on practice and CCG prescribing budgets, prescribers are asked to prescribe ISMN MR as one of the preferred low cost brands detailed above. For ISMN MR 60mg formulations, the preferred products are *Chemydur 60XL* tablets and *Monomil XL tablets*. Generic prescribing of ISMN MR or use of a high cost brand could increase Lincolnshire prescribing costs by as much as £64,000 in a quarter or £256,000 in a year. Following a lower cost strategy by prescribing preferred low cost brands will reduce this financial impact substantially.

Acknowledgements

This article is substantially based on work undertaken by the Trent Medicines Information Service that was published as part of the *Rapid Update on Supply Issues* series in February 2013.

NEW DRUG ASSESSMENT: SAXAGLIPTIN/METFORMIN TABLETS 2.5MG/850MG AND 2.5MG/1000MG (*KOMBOGLYZE*)

Komboglyze is a new saxagliptin/metformin combination product available in two different strengths of 2.5mg/850mg and 2.5mg/1000mg tablets. The product is licensed for the management of type 2 diabetes mellitus as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximum tolerated dose of metformin alone or those already being treated with a combination of saxagliptin and metformin. It is also indicated in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients when insulin and metformin alone do not provide adequate control.

PACEF have previously reviewed all four of the dipeptidylpeptidase-4 (DPP-4) inhibitors (saxagliptin, sitagliptin, linagliptin and vildagliptin) and have approved saxagliptin, sitagliptin and linagliptin for use within license and within the context of the NICE Clinical Guideline for the management of type 2 DM (see *PACE Bulletin* Vol 6 No 3 (January 2012) and NICE CG87 (May 2009)). All three agents are designated GREEN with sitagliptin recommended as the first line DPP-4 inhibitor of choice and saxagliptin acknowledged as a lower cost alternative; linagliptin (*Trajenta*) was approved as the preferable option in patients suffering from renal or hepatic impairment.

A cost comparison reveals the following:

Drug	Daily dose	Cost 28 days
Combination gliptin with metformin		
Saxagliptin 2.5mg/ metformin 850mg tablets *(Komboglyze)*	**One tablet twice daily**	**£31.60**
Saxagliptin 2.5mg/ metformin 1000mg tablets *(Komboglyze)*	**One tablet twice daily**	**£31.60**
Sitagliptin 50mg/ metformin 1000mg tablets (*Janumet*)	One tablet twice daily	£34.56
Linagliptin 2.5mg/ metformin 850mg tablets (*Jentadueto*)	One tablet twice daily	£33.26
Linagliptin 2.5mg/ metformin 1000mg tablets (*Jentadueto*)	One tablet twice daily	£33.26
Vildagliptin 50mg/ metformin 850mg tablets (*Eucreas*)	One tablet twice daily	£31.71
Vildagliptin 50mg/ metformin1000mg tablets (*Eucreas*)	One tablet twice daily	£31.71
Individual drugs		
Linagliptin 5mg tablets (*Trajenta*)	One tablet once daily	£33.26
Saxagliptin 5mg tablets (*Onglyza*)	**One tablet once daily**	**£31.60**
Sitagliptin 100mg tablets (*Januvia*)	One tablet once daily	£33.26
Vildagliptin 50mg tablets (*Galvus*)	50mg twice daily(with metformin or glitazone)	£31.76
Vildagliptin 50mg tablets (*Galvus*)	50mg daily (with sulfonylurea)	£15.85
Metformin 850mg tablets	**One tablet twice daily**	**£1.11**
Metformin 500mg tablets	**Two tablets twice daily**	**£3.08**

Saxagliptin remains the lowest cost DPP-4 inhibitor currently available. *Komboglyze* tablets (saxagliptin/metformin) are priced identically to single component saxagliptin, effectively providing the metformin component at no additional cost.

PACEF Recommendation:

PACEF have previously approved saxagliptin 5mg tablets (*Onglyza*) for use on the basis of the range of licensed indications and the lower cost compared to alternative DPP-4 inhibitors. As saxagliptin/metformin tablets 2.5mg/850mg and 2.5mg/1000mg tablets (*Komboglyze)* are comparably priced to the single component saxagliptin 5mg tablets (*Onglyza*), they are also approved for use and designated GREEN within licensed indications. Where combination DPP-4 inhibitor and metformin therapy is indicated, saxagliptin/metformin tablets (*Komboglyze*) present a lower cost alternative to the already approved sitagliptin/metformin combination product (*Janumet*) (also

designated GREEN). Both saxagliptin/metformin tablets (*Komboglyze*) and sitagliptin/metformin tablets (*Janumet*) are included on the *Joint Formulary*.

NEW DRUG ASSESSMENT: GLYCOPYRRONIUM BROMIDE INHALER (*SEEBRI BREEZHALER*)

Seebri Breezhaler is a recently launched inhaled formulation of glycopyrronium bromide licensed for maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). As an inhaled drug, glycopyrronium bromide is classified as a long-acting muscarinic antagonist (LAMA) and represents a possible alternative to tiotropium bromide (*Spiriva*) and aclidinium bromide (*Eklira Genuair*); both of these drugs are designated GREEN and are available through the Joint Formulary for maintenance treatment of COPD. Tiotropium bromide (*Spiriva*) is preferred as it is well established in therapy and associated with a broader evidence base; recent safety concerns related to the *Spiriva Respimat* device have resulted in the *Spiriva Handihaler* being preferred with aclidinium bromide (*Eklira Genuair*) advocated where the patient is intolerant of tiotropium or experiences problems with the *Handihaler* device (see *PACE Bulletin* Vol 7 No 2 (January 2013). In view of the mounting safety concerns, the *Spiriva Respimat* device has been designated RED-RED and should no longer be initiated in new patients; all new initiations of tiotropium should be for the *Handihaler* device. All existing patients continuing to use the *Respimat* device need to be reviewed and alternatives considered. PACEF considered all of this as context when reviewing glycopyrronium bromide (*Seebri Breezhaler*).

Glycopyrronium bromide is formulated as a dry powder in a hard capsule which is inhaled through the *Breezhaler* device which punctures the capsule to allow the dry powder to be inhaled. The clinical evidence supporting the use of the product is largely based on two registration (Phase 3) clinical trials known as GLOW 1 (appoximately 800 patients) and GLOW 2 (approximately 1000 patients). Both studies compared inhaled glycopyrronium bromide with placebo in adult patients aged 40 and over with moderate to severe COPD. The primary endpoint for both studies was change of trough FEV1 at 12 weeks compared to placebo. All other long-acting bronchodilator therapy was stopped, although inhaled corticosteroids and short acting beta$_2$ agonists could be continued. Both GLOW 1 and GLOW 2 improved trough FEV1 by approximately100ml which is normally accepted as the minimum required to achieve clinical significance. In terms of secondary outcomes, improvements in breathlessness and health status were seen statistically but were often not of clinical significance. There was some evidence to show reduction of exacerbations with glycopyrronium compared to placebo, but analysis was based on a maximum of one year's data which was insufficient to be conclusive. Both studies were for a maximum of 12 months and provided no categorical reassurance around long-term safety data. Safety concerns around the use of LAMAs are particularly acute at present due to the concerns over the safety of the *Spiriva Respimat* device.

GLOW2 also had an unblinded tiotropium arm which appeared to show comparable efficacy and safety for tiotropium and glycopyrronium.

A cost comparison with other available treatments reveals the following:

Drug	**Presentation**	**Dose**	**Cost per 30 days**
Formoterol	*Easyhaler Formoterol* 12mcg (120D)	12mcg bd	£11.88
	Atimos Modulite 12mcg (100D)	12mcg bd	£18.04
	Foradil 12mcg capsule for use in inhaler (60D)	12mcg bd	£23.38
	Oxis Turbohaler 12mcg (60D)	12mcg bd	£24.80
Glycopyrronium	***Seebri Breezhaler* capsules for use in inhaler 50mcg (30D)**	**44mcg once daily**	**£27.50**

Aclidinium	*Eklira Genuair* 400mcg (60D)	322mcg bd	£28.60
Salmeterol	*Neovent* 25mcg (120D)	50mcg bd	£29.26
	Serevent Evohaler 25mcg (120D)	50mcg bd	£29.26
	Serevent Accuhaler 50mcg (60D)	50mcg bd	£29.26
	Serevent Diskhaler 50mcg (60D)	50mcg bd	£35.79
Indacaterol	*Onbrez Breezhaler* capsules for use in inhaler 150mcg & 300mcg (60D)	150mcg bd 300mcg bd	£29.26 £29.26
Tiotropium	*Spiriva Handihaler* capsules for use in inhaler 18mcg (30D)	18mcg once daily	£34.87 (£33.50R)
	Spiriva Respimat 2.5mcg (60D)	5mcg once daily	£35.50

Key

Long-acting beta-agonist (LABA)	
Long-acting muscarinic antagonist (LAMA)	

R=Refill

PACEF Recommendation:

The evidence base for glycopyrronium bromide (*Seebri Breezhaler*) is greater than that for the other recently launched muscarinic antagonist: aclidinium bromide (*Eklira Genuair*), but is insufficient to establish evidence of overall superiority in efficacy or safety over tiotropium bromide. All that can be established from existing trial data is that glycopyrronium bromide (*Seebri Breezhaler*) is safe and effective in comparison to placebo for the 12 month duration of the trial. The unblinded tiotropium arm of the GLOW2 study suggests comparable efficacy and safety with tiotropium, but is not sufficiently robust data to support assumptions of direct equivalence or to justify therapeutic switching. Inhaled glycopyrronium bromide (*Seebri Breezhaler*) is the least expensive LAMA currently available and can be considered as a second line alternative to tiotropium bromide (*Spiriva*) or as a direct and lower cost alternative to aclidinium bromide (*Eklira Genuair*). It is specifically advocated where the patient is intolerant of tiotropium or experiences problems with the *Handihaler* device and is designated GREEN. All three of the inhaled LAMAs have now been approved for use through the Joint Formulary with tiotropium bromide (*Spiriva*) preferred first line.

NEW DRUG ASSESSMENT: ZONISAMIDE CAPSULES (*ZONEGRAN*)

Zonisamide (*Zonegran*) is an antiepileptic agent licensed for use as monotherapy or as adjunctive therapy in the treatment of partial seizures with or without secondary generalisation in adults.

NICE Clinical Guideline 137, *The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care* (January 2012), recommends that, if adjunctive treatment is ineffective or not tolerated, the patient should be discussed with, or referred to, a tertiary specialist who could consider clobazam, levetiracetam, topiramate or zonisamide. NICE have not yet considered zonisamide for monotherapy, although it has recently gained a marketing authorisation for this indication.

Both monotherapy and adjunctive therapy require a titration phase which is best managed under the supervision of the initiating specialist. Dosage adjustments need to be made when the patient is taking concurrent CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone and rifampicin).

Maintenance therapy with zonisamide (*Zonegran*) at a dose between 150mg twice daily and 250mg twice daily will cost between £110 and £172.48 per month.

PACEF Recommendation:
Zonisamide (*Zonegran*) capsules 25mg, 50mg and 100mg are designated AMBER without shared care and within licensed indications. The dose titration period, which can be anything from 5 to 10 weeks, depending on the indication and concurrent therapy, should be managed under the direct supervision of the initiating specialist. Zonisamide (*Zonegran*) capsules are approved for inclusion in the Joint Formulary.

NEW TRIAL ASSESSMENTS

RISK OF DEMENTIA WITH BENZODIAZEPINES

Ref: Billioti de Gage S et al. Benzodiazepine use and the risk of dementia: prospective population based study. *BMJ* 2012; 345:e6231 doi:10.1136/bmj.e6231

This French prospective cohort study followed 1,063 people aged over 65years (mean 78.2 years) who were free of dementia and did not start taking benzodiazepines until at least the third year of up to 15 years follow up. New use of benzodiazepines (between 3 to 5 yrs after enrolment) was associated with an increased risk of dementia (adjusted hazard ratio 1.60). Broadly similar results were found for first use of a benzodiazepine if started 8, 10, 13 or 15 years after enrolment.

EFFECTIVENESS OF NON-BENZODIAZEPINE HYPNOTICS IN THE TREATMENT OF ADULT INSOMNIA

Ref: Huedo-Medina TB et al. Effectiveness of non-benzodiazepine hypnotics in treatment of adult insomnia: meta-analysis of data submitted to the Food and Drug Administration. *BMJ* 2012;345:e8343 doi:10.1136/bmj.e8343

This is a meta-analysis of data submitted to the United States Food and Drug Administration (FDA) on the effectiveness of Z-drugs in 13 randomized controlled trials (n=4378). It found that Z drugs had a small but statistically significant improvement in sleep latency compared to placebo. No statistically significant effects were found on secondary outcomes, including total sleep time, sleep quality or number of wakenings.

PACEF Comment: These two studies reinforce longstanding national and local guidance on the use of hypnotics. One study confirms the limited effectiveness of Z drugs, whilst the other suggests a possible association between hypnotic use and dementia. It is possible that the results of this latter study reflect reverse causation (sleep disturbance may precede the diagnosis of dementia by a number of years) even though a 3 year window was used to ensure that early symptoms of dementia were not apparent. Given the more well established harms of these drugs (e.g. falls, accidents, cognitive impairment, dependence) hypnotics should be reserved for the short term relief of insomnia that is severe, disabling and causing unacceptable distress to patients.

INCREASED RISK OF NSAID INDUCED ACUTE KIDNEY INJURY IN PATIENTS TAKING CONCURRENT DIURETIC AND ACE INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKER THERAPY

Ref: Lapi F et al. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case control study. *BMJ* 2013;346:e8525 doi: 10.1136/bmj.e8525

Taking data from 487,372 users of antihypertensive medicines on the UK Clinical Practice Research Datalink (formerly known as General Practice Research Database), this nested case control study looked at the addition of NSAIDs to antihypertensive medicines and the occurrence of acute kidney injury (AKI). After a mean follow up of 6 years (2215 cases of AKI)

- the use of a diuretic and ACEI/ARB with a NSAID increased the risk of AKI by 31%. The highest risk was observed in the first 30 days.
- the use of either a diuretic or ACEI/ARB with NSAIDS was not associated with a statistically significant increased risk of AKI (although there is a suggestion of an early increase in risk for the diuretic – NSAID combination).

PACEF Comment: The findings of this study are not unexpected given the known renal toxicity of the 3 groups of medicines. But there is relatively little known about the effects of drug-drug interactions on acute kidney injury and the use of these groups of medicines is widespread, so this work is notable. It serves as a reminder to prescribers that increased vigilance is warranted when diuretics and ACEI/ARBs are used concurrently with NSAIDs, particularly during the first month of use. Although the study did not find an increased risk of acute kidney injury associated with NSAIDs and use of diuretics or ACEI/ARBs (dual therapy) this is not sufficiently robust evidence to demonstrate that the combination is without harm.

NICE TECHNOLOGY APPRAISAL 261: *RIVAROXABAN FOR THE TREATMENT OF DEEP VEIN THROMBOSIS AND PREVENTION OF RECURRENT DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM* (JULY 2012)

Key Recommendations

Rivaroxaban is recommended as an option for treating deep vein thrombosis and preventing recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE) after a diagnosis of acute deep vein thrombosis in adults.

PACEF Comment: Rivaroxaban (*Xarelto*) 15mg and 20mg film coated tablets are licensed for the treatment of DVT and PE and for the prevention of recurrent DVT and PE in adults; NICE have approved the drug for use as an option in these patients. Rivaroxaban has already been approved for use in county for use for the prophylaxis of venous thromboembolism following hip or knee replacement surgery following NICE approval in April 2009 (designation RED). It is also approved for use for the prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation following NICE approval in May 2012 (designation GREEN). PACEF are currently working in conjunction with ULH Drug and Therapeutics Committee and lead clinicians to develop supporting guidance for the implementation of this TA. During this interim period, rivaroxaban (*Xarelto*) 15mg and 20mg film coated tablets are designated RED for this indication and can only be prescribed by a specialist within secondary care. Possible AMBER or GREEN classification will be considered as part of the development of supporting guidance. The product will be added to the Joint Formulary for this indication.

NICE TECHNOLOGY APPRAISAL 264: *ALTEPLASE FOR TREATING ACUTE ISCHAEMIC STROKE* (REVIEW OF TECHNOLOGY APPRAISAL GUIDANCE 122)

Key Recommendations

Alteplase is recommended within its marketing authorisation for treating acute ischaemic stroke in adults if: (1) treatment is started as early as possible within 4.5 hours of onset of stroke symptoms, and (2) intracranial haemorrhage has been excluded by appropriate imaging techniques.

PACEF Recommendation:
Alteplase injection (*Actilyse*) is a well established component of post-stroke therapy. A UK marketing authorisation for alteplase to treat acute ischaemic stroke within three hours of the onset of symptoms was granted in September 2002. In March 2012 the MHRA extended the marketing authorisation to within 4.5 hours of onset of symptoms. NICE have reviewed the evidence and extended the treatment window to 4.5 hours in accordance with this license extention. Alteplase injection is already in use for this indication within ULH and the revised treatment window has already been implemented. Designation: RED. Alteplase injection (Actilyse) is already on the Joint Formulary for this indication.

NICE TECHNOLOGY APPRAISAL 265: *DENOSUMAB FOR THE PREVENTION OF SKELETAL-RELATED EVENTS IN ADULTS WITH BONE METASTASES FROM SOLID TUMOURS* (OCTOBER 2012)

Key Recommendations

Denosumab is recommended as an option for preventing skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from breast cancer and from solid tumours other than prostate if:

- bisphosphonates would otherwise be prescribed **and**
- the manufacturer provides denosumab with the discount agreed in the patient access scheme.

Denosumab is not recommended for preventing skeletal-related events in adults with bone metastases from prostate cancer.

PACEF Recommendation:
Denosumab injection (*XGEVA*) is designated as RED for the prevention of skeletal-related events in adults with bone metastases from breast cancer and from solid tumours. The prospect of formal shared care and an AMBER classification for these indications is under consideration, but not yet approved. Denosumab injection is a subcutaneous injection given in a dose of 120mg every four weeks. In theory, according to NICE, denosumab could be given in GP surgeries. It is less nephrotoxic than zoledronic acid and does not need monthly blood monitoring except in those with severe renal impairment. There is a higher incidence of hypocalcaemia and osteonecrosis of the jaw with denosumab than zoledronic acid. Denosumab injection (*XGEVA*) is designated RED-RED for the prevention of skeletal-related events in adults with bone metastases from prostate cancer as it is not considered cost-effective for this indication by NICE. Denosumab injection (*XGEVA*) is to be added to the Joint Formulary for the prevention of skeletal-related events in adults with bone metastases from breast cancer and from solid tumours only.

NICE TECHNOLOGY APPRAISAL 266: *MANNITOL DRY POWDER FOR INHALATION FOR TREATING CYSTIC FIBROSIS* (NOVEMBER 2012)

Key Recommendations

Mannitol dry powder for inhalation is recommended as an option for treating cystic fibrosis (CF) in adults: (1) who cannot use rhDNase (dornase alfa) because of ineligibility, intolerance or inadequate response to rhDNase **and** (2) whose lung function is rapidly

declining (forced expiratory volume in 1 second (FEV_1) decline greater then 2% annually) **and** for whom other osmotic agents are not considered appropriate.

Further Notes

Mannitol (*Bronchitol*) is a mucoactive agent that causes water to enter the airway lumen and hydrate airway secretions thereby increasing the clearance of secretions and pathogenic bacteria. It is inhaled from a hand-held, breath activated device. It holds a marketing authorisation for the treatment for CF in adults (aged 18 years and above) as an add-on therapy to best standard of care. The recommended dose is 400mg twice a day; this requires the inhalation of 10 capsules via the inhaler device twice a day.

The evidence supporting this TA comes from two randomised clinical trials DPM-CF-301 (295 patients) and DPM-CF-302 (305 patients). Both compared 400mg twice daily mannitol with 50mg twice daily mannitol (assumed to be sub-therapeutic). Patients in both arms received best supportive care with or without dornase alfa. Best supportive care included inhaled antibiotics, anti-inflammatory agents, bronchodilators, vitamin supplements, pancreatic enzymes and antidiabetic agents for those with diabetes. NICE concluded that these studies provided evidence of clinical-effectiveness measured in terms of improvement in lung function (FEV1) and reduced pulmonary exacerbations. They defined subgroups of patients who may experience greater benefit, specifically those who cannot use dornase alfa.
NICE concluded that mannitol was cost-effective in a sub-group of patients with a rapid decline in lung function who cannot use dornase alfa (*Pulmozyme*) because of ineligibility, intolerance or inadequate response which cannot be met with alternative therapies.

In terms of cost, mannitol dry powder for inhalation (*Bronchitol*) is comparable to dornase alfa (*Pulmozyme*).

	Dose	28 day cost
Mannitol dry powder for inhalation (*Bronchitol*)	400mg twice daily by inhalation	£463.32
Dornase alfa 2.5mg inhalation (*Pulmozyme*)	2.5mg once daily by inhalation	£462.40

PACEF Recommendation:
Mannitol dry powder for inhalation (*Bronchitol*) must only be initiated under the supervision and monitoring of an experienced physician or another healthcare professional appropriately trained and equipped to perform spirometry, monitor oxygen saturation and manage acute bronchospasm (including appropriate use of resuscitation equipment). There must be an initiation dose assessment before commencing treatment and all patients should be assessed for bronchial hyper-responsiveness to inhaled mannitol. PACEF concluded that mannitol dry powder for inhalation (*Bronchitol*) should be designated RED at this stage with the prospect for future consideration of AMBER (with shared care) in consultation with specialist services; it will be added to the Joint Formulary for this indication.

NICE TECHNOLOGY APPRAISAL 267: *IVABRADINE FOR TREATING CHRONIC HEART FAILURE* (NOVEMBER 2012)

Key Recommendations

Ivabradine is recommended as an option for treating chronic heart failure for people:

- with New York Heart Association (NYHA) class II stable chronic heart failure with systolic dysfunction and

- who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more and
- who are given ivabradine in combination with standard therapy including beta-blocker (BB) therapy, angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists, or when BB therapy is contraindicated or not tolerated and
- with a left ventricular ejection fraction of 35% or less.

Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, BBs and aldosterone antagonists. It should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. Dose titration and monitoring should be carried out by a heart failure specialist or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

PACEF Recommendation:
This NICE appraisal of a post hoc analysis of the SHIFT study consolidates the current PACEF position on ivabradine in chronic heart failure. Ivabradine tablets 5mg and 7.5mg (*Procoralan*) may be an appropriate adjunct to optimal beta blocker (BB)/ACE inhibitor therapy in patients unable to achieve sufficient heart rate reduction on standard therapy or for those in whom BBs are not tolerated or contraindicated and who still have a high pulse rate. As a result of this, ivabradine is approved for the treatment of CHF within the terms of its marketing authorisation (i.e. for stable CHF (NYHA class II to IV) with systolic dysfunction in patients in sinus rhythm with heart rate ≥75 beats per minute (bpm) in combination with a beta-blocker (BB) or when BB therapy is contraindicated or not tolerated). Treatment should only be initiated by a physician who is experienced in the management of heart failure. Designation: AMBER (without shared care). Ivabradine (*Procoralan*) is already approved for use on the Joint Formulary for this indication; it is also approved for use within license for chronic stable angina.

NICE TECHNOLOGY APPRAISAL 268: *IPILIMUMAB FOR PREVIOUSLY TREATED ADVANCE (UNRESECTABLE OR METASTATIC MELANOMA)* (DECEMBER 2012)

Key Recommendation

Ipilimumab is recommended as an option for treating advanced (unresectable or metastic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.

PACEF Recommendation:
Ipilimumab infusion (*Yervoy*) is licensed for the treatment of advanced unresectable or metastatic melanoma, following prior therapy. It is designated RED for this indication and will be added to the Joint Formulary.

NICE TECHNOLOGY APPRAISAL 269: *VEMURAFENIB FOR TREATING LOCALLY ADVANCED OR METASTATIC BRAF V600 MUTATION-POSITIVE MALIGNANAT MELANOMA* (DECEMBER 2012)

Vemurafenib is recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme.

PACEF Recommendation:
Vemurafenib tablets 240mg (*Zelboraf*) have a marketing authorisation for BRAF V600 mutation-positive unresectable or metastatic melanoma. Vemurafenib tablets 240mg (*Zelboraf*) are designated RED for this indication.

NICE TECHNOLOGY APPRAISAL 270: *DECITABINE FOR THE TREATMENT OF ACUTE MYELOID LEUKAEMIA (TERMINATED APPRAISAL)* (DECEMBER 2012)

NICE is unable to make a recommendation about the use in the NHS of decitabine for acute myeloid leukaemia (AML) because no evidence submission was received from the manufacturer.

PACEF Recommendation:
Decitabine infusion (*Dacogen*) is designated RED-RED for this indication.

Acknowledgements

Many thanks to Cathy Johnson, Interface Lead Pharmacist, NHSL, Robyn Thompson, Senior Pharmacist, ULH, Peter Richards, Prescribing Adviser, NHSL and Vanessa Chapman from the Trent Medicines Information Service for their help with the compilation of this *Bulletin*.

Stephen Gibson
Head of Prescribing and Medicines Optimisation
NHS Lincolnshire

March 2013