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

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 9; Number 8 **May 2015**

What's new this month?

- **ACBS approved sunscreen preparations can only be prescribed for ACBS approved indications (i.e. protection from UV radiation in abnormal cutaneous photosensitivity resulting from genetic disorders or photodermatoses, including vitiligo and those resulting from radiotherapy; and chronic or recurrent herpes simplex labialis). Within this context, *Anthelios SPF 50+ Melt In Cream*, *Sunsense Ultra SPF 50+* lotion, *Uvistat Lipscreen SPF 50* lip protector, *Uvistat Suncream* SPF 30 and *Uvistat Suncream* SPF 50 are all designated GREEN. Prescribers are advised to resist patient or care home requests to prescribe sunscreens for any other indication or patient group. Outside of ACBS approved indications, and in common with the rest of the population, when a sunscreen is indicated patients should purchase their own supply (see page 4).**
- ***Bexsero* is the first vaccine authorised in the UK for immunisation against invasive meningococcal disease caused by *Neisseria meningitidis* group B. Prescribers are reminded that meningococcal group B vaccine (*Bexsero*) is currently designated RED-RED, although this will be subject to change once the national vaccination programme begins later in the year. Until then, the vaccine should only be prescribed for the management of outbreaks of invasive meningococcal disease where the vaccine may be prescribed for close contacts of cases following a request from a PHE consultant or nurse. The product may also be indicated in the same high risk groups that are currently offered ACWY conjugate vaccine. All patient, parent or carer requests outside of these indications should be refused pending the introduction of the national vaccination programme (see page 5).**
- ***theiCal-D3* once daily chewable tablets (calcium 1g/vitamin D3 880i.u.) are designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary* within licensed indications (see page 5).**
- ***Calcichew D3 1g/800iu Once Daily* chewable tablets are premium price and significantly higher in cost than most alternative calcium and vitamin D3 combination products. They are designated RED-RED and have not been approved for inclusion in the *Joint Formulary*. Where an evidence based once daily calcium and vitamin D supplement is required, *theiCal-D3* chewable tablets should be prescribed (see page 5).**
- **PACEF guidance on the use of calcium and vitamin D supplementation has been updated (see page 5).**
- **Methylphenidate hydrochloride 18mg and 36mg sustained release tablets (*Xenidate XL*) are designated AMBER with shared care and approved for inclusion in the *Lincolnshire Joint Formulary* within licensed indications. Product switching from *Concerta XL*/generic SR 18mg and 36mg tablets to branded *Xenidate XL* 18mg and 36mg SR tablets has been included in the *CCG Prescribing QIPP Programme for 2015/16*. The potential saving across the Lincolnshire Clinical Commissioning Groups is £61,239pa (see page 7).**
- **Tolterodine tartrate 2mg and 4mg sustained release capsules (*Neditol XL*) are designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*. Product switching from *Detrusitol XL*/generic SR 4mg tablets to branded *Neditol XL* 4mg SR tablets has been included in the *CCG Prescribing QIPP Programme for 2015/16*. The potential saving across the Lincolnshire Clinical Commissioning Groups is £149,586pa (see page 7).**

- **Brimonidine tartrate 3mg/g gel (*Mirvaso*) is the first treatment to be licensed specifically for facial erythema in rosacea. After a review of the most up to date evidence and specialist guidance, the product has been re-designated from RED-RED to AMBER without shared care for initiation by a dermatologist only. Its use should be restricted to patients with moderate to severe persistent erythema of rosacea that is causing significant psychological or social distress. It is approved for inclusion in the *Lincolnshire Joint Formulary* within license and subject to agreed criteria (see page 8).**

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SUMMARY OF PACEF DECISIONS: *APRIL 2015 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Adalimumab injection (*Humira*) (AbbVie)	For the treatment of moderately to severely active ulcerative colitis in adults.	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Anthelios SPF 50+ Melt In Cream (La Roche-Posay)	For protection from UV radiation in abnormal cutaneous photosensitivity resulting from genetic disorders or photo-dermatoses, including vitiligo and those resulting from radiotherapy. For chronic or recurrent herpes simplex labialis.	GREEN Subject to ACBS restricted indications (*Drug Tariff* Part XV Borderline Substances). Included in the *Lincolnshire Joint Formulary* for these restricted indications. . Sunscreens should not be prescribed for any other indication.
Axitinib 1mg and 5mg tablets (*Inlyta*)	For the treatment of adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib and cytokine	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Brimonidine tartrate 3mg/g gel *(Mirvaso)* *(*Galderma)	Symptomatic treatment of facial erythema due to rosacea	AMBER without shared care. Approved for inclusion in the *Lincolnshire Joint Formulary*. Restricted to patients with moderate to severe persistent erythema of rosacea that is causing significant psychological or social distress.

Calcichew D3 1g/800iu Once Daily chewable tablets (calcium 1g/ Vit D 800i.u.) (Takeda)	For the prevention and treatment of vitamin D and calcium deficiency in the elderly and as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency.	RED-RED. Not approved for inclusion in the *Lincolnshire Joint Formulary*
Colesevelam 625mg capsules (*Cholestagel*) (Genzyme)	Adjunct to diet in primary hypercholesterolaemia either with a statin for patients inadequately controlled on statin alone or as monotherapy when a statin is inappropriate or not tolerated. Adjunct to ezetimibe with or without a statin in primary hyper cholesterolaemia.	RED-RED. Not approved for inclusion in the *Lincolnshire Joint Formulary*
Colesevelam 625mg capsules (*Cholestagel*) (Genzyme)	For the treatment of chronic diarrhoea or intractable pruritis in patients with bile acid malabsorption, second line after cholestyramine. For the treatment of diarrhoea caused by lenalidomide	AMBER without shared care. Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. Should be used second line after cholestyramine. AMBER without shared care. Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. Should be used second line after cholestyramine.
Golimumab injection (*Simponi)* (MSD)	For the treatment of moderately to severely active ulcerative colitis in adults.	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Infliximab intravenous infusion (*Remicade*/*Inflectra*/*Remsima*)	For the treatment of moderately to severely active ulcerative colitis in adults. For the treatment of severely active ulcerative colitis in children and young people aged 6 to17.	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for these indications.
Meningococcal group B vaccine (*Bexsero*) (Novartis Vaccines)	For active immunisation against invasive disease cause by *Neisseria meningitidis* group B.	RED-RED. Should only be prescribed on the NHS for the management of outbreaks of invasive meningococcal disease where the vaccine may be prescribed for close contacts of cases following a request from a Public Health England consultant or nurse. May also be indicated in the same high risk groups that are currently offered ACWY conjugate vaccine.
Methylphenidate hydrochloride 18mg and 36mg sustained release tablets (*Xenidate XL*) (Mylan)	For attention deficit hyperactivity disorder (ADHD) in children aged 6 and over. Continuing treatment into adulthood may be appropriate if symptoms persist and there has been clear benefit from treatment in adolescence.	AMBER with shared care. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Regorafenib 40mg tablets (*Stivarga*)	For the treatment of metastatic colorectal cancer after metastatic disease.	RED-RED Not improved for inclusion in the *Lincolnshire Joint Formulary*.
Sunsense Ultra SPF 50+ lotion (Crawford)	For protection from UV radiation in abnormal cutaneous photosensitivity resulting from genetic disorders or photo-dermatoses, including vitiligo and those resulting from radiotherapy. For chronic or recurrent herpes simplex labialis.	GREEN Subject to ACBS restricted indications (*Drug Tariff* Part XV Borderline Substances). Included in the *Lincolnshire Joint Formulary* for these restricted indications. Sunscreens should not be prescribed for any other indication.
theiCal-D3 chewable tablets (calcium 1g/vit D3 880i.u.) (Stirling Anglian)	For the prevention and treatment of vitamin D and calcium deficiency in the elderly and as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency.	GREEN Included in the *Lincolnshire Joint Formulary*. Preferred chewable once daily preparation.
Tolterodine tartrate 2mg and 4mg sustained release	For the symptomatic treatment of urge incontinence and/or increased	GREEN Included in the *Lincolnshire Joint*

capsules (*Neditol XL*) (Aspire)	urinary frequency and urgency as may occur in patients with overactive bladder syndrome.	*Formulary*.
Uvistat Lipscreen SPF 50 lip protector (Boston Healthcare) *Uvistat* Suncream SPF 30 sun cream (Boston Healthcare) *Uvistat* Suncream SPF 50 sun cream (Boston Healthcare)	For protection from UV radiation in abnormal cutaneous photosensitivity resulting from genetic disorders or photo-dermatoses, including vitiligo and those resulting from radiotherapy. For chronic or recurrent herpes simplex labialis.	GREEN Subject to ACBS restricted indications (*Drug Tariff* Part XV Borderline Substances). Included in the *Lincolnshire Joint Formulary* for these restricted indications. Sunscreens should not be prescribed for any other indication.

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

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

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PRESCRIBING SUNSCREENS

Sunscreens can only be prescribed on FP10 prescription if they are ACBS approved and for approved indications.

Some practices are reporting approaches from care homes asking for sunscreens to be prescribed for their residents on FP10 over the summer period. The *Drug Tariff* is quite specific on the sunscreens that are available on the NHS and the indications for which they can be used. The ACBS approved indications are:

- protection from UV radiation in abnormal cutaneous photosensitivity resulting from genetic disorders or photodermatoses, including vitiligo and those resulting from radiotherapy.
- chronic or recurrent herpes simplex labialis.

The only products available on prescription for these indications are:

- *Anthelios SPF 50+ Melt In Cream*
- *Sunsense Ultra SPF 50+* lotion
- *Uvistat* Lipscreen SPF 50 lip protector
- *Uvistat* Suncream SPF 30 sun cream
- *Uvistat* Suncream SPF 50 sun cream

PACEF Recommendation:
ACBS approved sunscreen preparations can only be prescribed for ACBS approved indications (i.e. protection from UV radiation in abnormal cutaneous photosensitivity resulting from genetic disorders or photodermatoses, including vitiligo and those resulting from radiotherapy; and chronic or recurrent herpes simplex labialis). Within this context, *Anthelios SPF 50+ Melt In Cream*, *Sunsense Ultra SPF 50+* lotion, *Uvistat* Lipscreen SPF 50 lip protector, *Uvistat* Suncream SPF 30 and *Uvistat* Suncream SPF 50 are designated GREEN. Prescribers are advised to resist patient or care home requests to prescribe sunscreens for any other indication or patient group. Outside of

ACBS approved indications, and in common with the rest of the population, when a sunscreen is indicated patients should purchase their own supply.

PRESCRIBING MENINGOCOCCAL GROUP B VACCINE (BEXSERO)

Meningococcal group B vaccine (*Bexsero*) is currently designated RED-RED and should only be prescribed on the NHS in exceptional circumstances. A national vaccination programme is due to begin later in the year.

Bexsero is the first vaccine authorised in the UK for immunisation against invasive meningococcal disease caused by *Neisseria meningitidis* group B. Prescribers are reminded that meningococcal group B vaccine (*Bexsero*) is currently designated RED-RED, although this will be subject to change once the national vaccination programme begins later in the year. Until then, the vaccine should only be prescribed on the NHS for the management of outbreaks of invasive meningococcal disease where the vaccine may be prescribed for close contacts of cases following a request from a Public Health England consultant or nurse. The product may also be indicated in the same high risk groups that are currently offered ACWY conjugate vaccine as listed in the Green Book. These include: asplenic patients, those with splenic dysfunction, those with complement disorders and those who are at risk of exposure to meningitis B through their occupation (for example, laboratory workers). All patient, parent or carer requests outside of these indications should be refused pending the introduction of the national vaccination programme; however, practices can contact a member of NHSE Public Health department for advice if they feel there is a need to vaccinate a patient outside of the Green Book recommendations.

RAPID DRUG ASSESSMENTS: *CALCICHEW D3 1G/800 UNIT ONCE DAILY CHEWABLE TABLETS/ THEICAL D3 CHEWABLE TABLETS*

Where an evidence based, once daily calcium and vitamin D supplement is required, *theiCal-D3* chewable tablets should be preferred.

Both *Calcichew D3 1g/800iu Once Daily chewable tablets* and *theiCal-D3* chewable tablets are new calcium and vitamin D combination products licensed for the prevention and treatment of vitamin D and calcium deficiency in the elderly and as an adjunct to specific osteoporosis treatment of patients who are at risk of vitamin D and calcium deficiency. Each product contains an evidence based dose of calcium and vitamin D3 for the prevention of hip fracture, non-vertebral fracture and falls (i.e. at least 1000mg of calcium and 800iu of vitamin D daily). In addition, both products offer a once daily option compared to the standard twice daily regimens of established products.

An updated cost comparison of all of the evidence based calcium and vitamin D products reveals that *Calcichew D3 1g/800iu Once Daily* chewable tablets are high cost in comparison to twice daily alternatives. Conversely, *theiCal-D3* chewable tablets (calcium 1g/vit D3 880i.u.) emerge as competitively priced even against the lower cost twice daily formulations. Both products are formulated with citrus flavours to improve palatability.

Product	Dose	Price (28 days)	Flavour
***Accrete D3* tablets (calcium 600mg/vit D 400i.u.)**	**1 tablet twice daily**	**£2.76**	
***Adcal –D3* chewable tablets (calcium 600mg/ vit D 400i.u.)**	**1 tablet twice daily**	**£3.65**	**Lemon or Fruit**
***Adcal D3 Caplets* (calcium 300mg/vit D 200i.u.)**	**2 tablets twice daily**	**£3.65**	
Adcal-D3 Dissolve Effervescent tablets (calcium 600mg/vit D 400i.u.)	1 tablet twice daily	£5.99	Lemon
Cacit D3 effervescent granules	2 sachets daily	£7.58	Lemon

(calcium 500mg/ vit D 440i.u.)			
***Calceos* chewable tabs (Calcium 500mg/ vit D 400i.u.)**	**1 tablet twice daily**	**£3.34**	**Lemon**
Calcichew D3 Forte chewable tablets (calcium 500mg, Vit D 400i.u.)	1 tablet twice daily	£3.96	Lemon
Calcichew D3 500mg/400iu Caplets (calcium 500mg, Vit D 400i.u.)	1 tablet twice daily	£4.16	
Calcichew D3 1g/800iu Once Daily chewable tablets (calcium 1g, Vit D 800i.u.)	1 tablet daily	£6.30	Lemon
Calfovit D3 sachets (calcium 1200mg/Vit D3 800i.u.)	1 sachet daily	£4.04	Lemon
Evacal D3 chewable tablets (calcium 600mg/vit D3 400i.u.)	1 tablet twice daily	£2.92	
Natecal D3 chewable tablets (calcium 600mg/vit D3 400i.u.)	**1 tablet twice daily**	**£3.39**	**Aniseed/peppermint**
***theiCal-D3* chewable tablets (calcium 1g/vit D3 880i.u.)**	**1 tablet daily**	**£2.76**	**Orange**

Formulary approved products are in featured in **bold.**
Reference: *MIMS* March 2015.

PACEF Recommendation:
***theiCal-D3* once daily chewable tablets (calcium 1g/vit D3 880i.u.) are designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary* within licensed indications. *Calcichew D3 1g/800iu Once Daily* chewable tablets are premium price and significantly higher in cost than most alternative calcium and vitamin D3 combination products. They are designated RED-RED and have not been approved for inclusion in the *Joint Formulary*. Where an evidence based, once daily calcium and vitamin D supplement is required, *theiCal-D3* chewable tablets should be prescribed (see page). PACEF guidance on the use of calcium and vitamin D supplementation is updated below.**

UPDATED PACEF GUIDANCE ON CALCIUM AND VITAMIN D SUPPLEMENTATION

(1) There is strong evidence to suggest that elderly people living in institutionalised care are likely to benefit from calcium and vitamin D supplementation. The best evidence is around daily doses of 1200mg of calcium and 800iu of vitamin D. Evidence suggests that this can significantly reduce the risk of hip fracture, non-vertebral fracture and falls. It is strongly recommended that all ambulatory patients over the age of 65 currently resident in sheltered accommodation or care homes should be prescribed calcium and vitamin D. Prescribers are encouraged to review all patients in care homes and sheltered accommodation to ensure that calcium and vitamin D supplementation is prescribed for the ambulatory over 65s unless there are compelling reasons not to do so.
(2) Calcium and vitamin D should be prescribed for people on or commencing systemic corticosteroid therapy at any dose for 3 months or longer.
(3) All women on treatment for the primary or secondary prevention of osteoporotic fragility fractures should be prescribed calcium and vitamin D unless dietary intake is considered to be adequate.
(4) Only calcium and vitamin D formulations containing an evidence based dose of each component should be prescribed (i.e. at least 1000mg of calcium and 800iu of vitamin D daily). First line preferred products are *Accrete D3 tablets*, *Adcal D3 Chewable* tablets, *Adcal D3* caplets, *Calceos Chewable* tablets, *Natecal D3* chewable tablets (all twice daily) and *theiCal-D3* chewable tablets (once daily).

RAPID DRUG ASSESSMENT: *METHYLPHENIDATE 18MG AND 36MG SUSTAINED RELEASE TABLETS (XENIDATE XL)*

Methylphenidate hydrochloride 18mg and 36mg sustained release tablets (*Xenidate XL*) (Mylan) are licensed for attention deficit hyperactivity disorder (ADHD) in children of 6 and over. Continuing treatment into adulthood may be appropriate if symptoms persist and there has been clear benefit from treatment in adolescence. *Xenidate XL tablets* have the same marketing authorisation as the other equivalent dose sustained release formulations currently available, *Concerta XL* (Janssen Cilag) and *Matoride XL* (Sandoz).

A cost comparison reveals that *Xenidate XL* is significantly lower in cost that *Concerta XL* or Matoride XL:

Methylphenidate sustained release preparation	**Dose**	**Cost (£) 30 days**
Methylphenidate 18mg sustained release tablet (*Concerta XL*)	18mg once daily	£31.19
Methylphenidate 36mg sustained release tablet (*Concerta XL*)	36mg once daily	£42.45
Methylphenidate 18mg sustained release tablet (*Matoride XL*)	18mg once daily	£24.95
Methylphenidate 36mg sustained release tablet (*Matoride XL*)	36mg once daily	£33.96
Methylphenidate 18mg sustained release tablet (*Xenidate XL*)	18mg once daily	£20.27
Methylphenidate 36mg sustained release tablet (*Xenidate XL*)	36mg once daily	£27.59

There are significant savings if *Xenidate XL* is prescribed by brand as the preferred 18mg and 36mg sustained release formulation:

CCG	**Potential Annual Saving (assuming 100% switch)**
LECCG	£17,851
LWCCG	£20,680
SLCCG	£10,132
SWLCCG	£12,576
Lincolnshire	£61,239

PACEF Recommendation:

Methylphenidate hydrochloride 18mg and 36mg sustained release tablets (*Xenidate XL*) are designated AMBER with shared care and approved for inclusion in the *Lincolnshire Joint Formulary* within licensed indications. Product switching from *Concerta XL*/generic SR 18mg and 36mg tablets to branded *Xenidate XL* 18mg and 36mg SR tablets has been included in the *CCG Prescribing QIPP Programme for 2015/16*. The potential saving across the Lincolnshire Clinical Commissioning Groups is £61,239pa.

RAPID DRUG ASSESSMENT: *TOLTERODINE 4MG SUSTAINED RELEASE CAPSULE (NEDITOL XL)*

Tolterodine tartrate 2mg and 4mg sustained release capsules (*Neditol XL*) (Aspire) are licensed for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency in patients with overactive bladder syndrome. *Neditol XL* holds the same marketing authorisation as the alternative sustained release formulation and originator

brand, *Detrusitol XL.* A cost comparison reveals that *Neditol XL* 4mg is significantly lower in cost than equivalent dose *Detrusitol XL*; both products are premium price compared to standard generic twice daily tolterodine:

Tolterodine preparation	**Dose**	**Cost (£) 28 days**
Tolterodine 1mg tablets (generic)	1mg twice daily	£2.56
Tolterodine 2mg tablets (generic)	2mg twice daily	£2.88
Tolterodine 1mg tablets (*Detrusitol*)	1mg twice daily	£29.03
Tolterodine 2mg tablets (*Detrusitol*)	2mg twice daily	£30.56
Tolterodine tartrate 4mg sustained release capsules (*Detrusitol XL*)	4mg daily	£25.78
Tolterodine tartrate 2mg sustained release capsules (*Neditol XL*)	2mg daily	£11.60
Tolterodine tartrate 4mg sustained release capsules (*Neditol XL*)	4mg daily	£12.89

There are significant savings if tolterodine tartrate 4mg sustained release capsules (*Neditol XL*) are prescribed by brand as an alternative to generic prescriptions for tolterodine tartrate 4mg sustained release capsules and *Detrusitoil XL* 4mg:

	Potential annual saving (assuming 100% switch)
LECCG	£44,305
LWCCG	£41,940
SLCCG	£36,469
SWLCCG	£26,872
Lincolnshire	£149,586

PACEF Recommendation:
Tolterodine tartrate 2mg and 4mg sustained release capsules (*Neditol XL*) are designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*. Product switching from *Detrusitol XL*/generic SR 4mg tablets to branded *Neditol XL* 4mg SR tablets has been included in the *CCG Prescribing QIPP Programme for 2015/16*. The potential saving across the Lincolnshire Clinical Commissioning Groups is £149,586pa.

REVIEW: *BRIMONIDINE 3MG/G GEL (MIRVASO)*

(This is an updated version of a New Product Assessment originally published in *PACE Bulletin* Vol 8 No 13 (July 2014). New text is in bold)

Brimonidine tartrate 3mg/g gel (*Mirvaso*) is the first treatment to be licensed specifically for the treatment of facial erythema in rosacea. After a review of current guidance, the product has been re-designated as AMBER without shared care for initiation by a dermatologist only.

Rosacea is a chronic relapsing disease of facial skin, characterised by recurrent episodes of facial flushing, persistent erythema, telangiectasia (fine, dilated blood vessels), papules and pustules. For the symptoms of flushing and erythema (without papules and pustules) there is historically no effective treatment in primary care and management consists of lifestyle advice, including applying sunscreen and avoiding trigger factors.

Brimonidine tartrate 3mg/g gel (*Mirvaso*) holds a marketing authorisation for the symptomatic treatment of facial erythema due to rosacea in adults (i.e. those over 18); it is the first treatment to be authorised specifically for this indication. Alternative treatments (including short courses of oral tetracyclines, low dose erythromycin, topical formulations of

metronidazole (*Metrogel*, *Metrosa*, *Rosiced*, *Rozex, Zyomet*) and azelaic acid 15% gel (*Finacea*)) tend to hold marketing authorisations for either rosacea or for the topical treatment of papulopustular rosacea.

Supporting evidence for the use of brimonidine tartrate 3mg/g gel (*Mirvaso*) comes from two short-term (28 day) randomised placebo controlled trials. Both trials demonstrate that *Mirvaso* is more effective than vehicle gel alone at reducing erythema in people with a clinical diagnosis of rosacea and moderate to severe erythema. Success rates (defined as a 2 grade reduction in the severity of erythema as defined by patients and clinicians) were 25-30% with brimonidine gel compared to 10% with placebo. Some response (defined as 1 grade reduction in severity of erythema) was seen in 70% of the brimonidine gel group compared to a particularly strong placebo response of 30 to 40%. There are no published trials comparing *Mirvaso* with any pharmacologically active alternative. There is no long-term efficacy or safety data, although the manufacturer is promoting the product for on-going symptomatic treatment over a potentially long period. Brimonidine gel was found to act rapidly in trials (i.e. within 30minutes in 28% of patients with the effect partially maintained over a 12 hour period). The gel can be applied as required up to a maximum frequency of once daily.

PACEF recognise that there is currently no alternative or effective treatment for erythema in rosacea other than brimonidine gel. Existing treatment options, such as oral tetracyclines, are primarily used for the reduction of the inflammatory lesions of papulopustular rosacea, although some reduction in erythema may occur. Although effective when used short term, tetracyclines and other broad spectrum antibiotics carry with them the risk of increasing bacterial resistance, particularly if over used.

Adverse effects commonly associated with *Mirvaso* treatment include: erythema, pruritus and a burning sensation in the skin. Results from a longer term safety and efficacy study suggest that adverse effects do not worsen with longer treatment. As brimonidine is a highly selective alpha-adrenergic receptor agonist there is a potential for interaction with drugs affecting noradrenergic transmission (e.g. monoamine oxidase inhibitors, tricyclic antidepressants) and also in patients susceptible to the effects of alpha-adrenergic receptor agonists, such as those with cardiovascular disease, depression, cerebral or coronary insufficiency, Raynaud's phenomenon or orthostatic hypotension.

NICE published an evidence summary for new medicines covering the use of brimonidine gel after the *PACE Bulletin* assessment was published July 2014. NICE concluded that, whilst there is evidence to demonstrate effectiveness, the response rates reported from the trials were relatively low and improvements appeared to be transient. Brimonidine gel does not alter the course of the disease or have any effect on other features of rosacea, such as telangiectasia or inflammatory papules. It can be used up to once per day, but does not need to be used daily. Some specialists have suggested that patients may wish to restrict use of brimonidine gel to days when they are particularly self-conscious about their appearance.

The Scottish Medicines Consortium published their review of brimonidine gel in January 2015. The product was approved for restricted use within NHS Scotland for patients with moderate to severe persistent facial erythema associated with rosacea. The SMC also noted the relatively low response rates to the treatment but highlighted the lack of alternative treatment options for the management of this condition.

A cost comparison reveals that brimonidine 3mg/g gel (*Mirvaso*) is significantly higher in cost than any other alternative:

Drug	Authorised indication	Daily dose range	Cost (£) 28 days
Brimonidine 3mg/g gel (*Mirvaso*)	**Symptomatic treatment of facial erythema due to rosacea**	**Apply once daily**	**£33.69 (30g)**
Oral antibiotics			
Oxytetracyline 250mg tablets	Rosacea	500mg twice daily	£4.56
Tetracycline 250mg tablets	Rosacea	500mg twice daily	£9.84
Erythromycin 250mg tablets/capsules	Rosacea	500mg twice daily	£6.44
Doxycycline 100mg capsules	Unlicensed	100mg once daily	£3.68
Doxycycline 40mg MR capsules (*Efracea*)	Facial rosacea	40mg daily	£15.98
Other topical preparations			
Azelaic acid 15% gel (*Finacea*)	Papulopustular rosacea	Twice daily	£7.48 (30g)
Metronidazole 0.75% aqueous gel (*Metrogel*)	Acute inflammatory exacerbations of rosacea	Twice daily	£22.63 (40g)
Metronidazole 0.75% aqueous gel (*Metrosa*)	Acute inflammatory exacerbations of rosacea	Twice daily	£12.00 (30g) £19.90 (40g)
Metronidazole 0.75% cream (*Rosiced)*	Treatment of inflammatory papulo-pustules of rosacea	Twice daily	£7.50 (30g)
Metronidazole 0.75% aqueous gel (*Rozex)*	Treatment of inflammatory papules, pustules and erythema of rosacea	Twice daily	£6.60 (30g) £9.88 (40g)
Metronidazole 0.75% cream (*Rozex)*	Treatment of inflammatory papules, pustules and erythema of rosacea	Twice daily	£6.60 (30g) £9.88 (40g)
Metronidazole 0.75% gel (*Zyomet*)	Rosacea	Twice daily	£12.00 (30g)
Camouflagers			
Covermark foundation		Apply daily	£11.86(15ml)
Dermablend		Apply daily	£5.60 (12g)

PACEF Recommendation:
Brimonidine tartrate 3mg/g gel (*Mirvaso*) is the first treatment to be licensed specifically for facial erythema in rosacea and is the only effective treatment currently available. After a review of the most up to date evidence and guidance, the product has been re-designated as AMBER without shared care for initiation by a dermatologist only. Its use should be restricted to patients with moderate to severe persistent erythema of rosacea that is causing significant psychological or social distress. It is approved for inclusion in the *Lincolnshire Joint Formulary* within license and subject to agreed criteria.

RAPID DRUG ASSESSMENT: *COLESEVELAM 625MG CAPSULES (CHOLESTAGEL) FOR LENALIDOMIDE INDUCED DIARRHOEA*

Colesevelam (*Cholestagel*) is licensed solely for the treatment of primary and familial hypercholesterolaemia. It is a bile acid sequestrant that acts by binding bile acids and preventing their reabsorption. Although colesevelam has never been approved for use in Lincolnshire for its licensed indications, it has been approved for the treatment of chronic diarrhoea or intractable pruritis in patients with bile acid malabsorption, second line after cholestyramine. PACEF and United Lincolnshire Hospitals Drug and Therapeutics Committee considered an application from ULH Haematology to extend this role to include diarrhoea caused by lenalidomide (also thought to be linked to bile acid malabsorption).

PACEF Recommendation:
Colesevelam 625mg capsules (*Cholestagel*) are approved for use for the treatment of chronic diarrhoea or intractable pruritis in patients with bile acid malabsorption second line after cholestyramine. After a review of the evidence, PACEF have approved an application from ULH Haematology to extend this to include diarrhoea caused by lenalidomide; designation AMBER without shared care. It was agreed that the list of indications on *Formulary* would be extended to include diarrhoea caused by lenalidomide with the stipulation that this is second line after cholestyramine.

NICE TECHNOLOGY APPRAISAL 329: *INFLIXIMAB, ADALIMUMAB AND GOLIMUMAB FOR TREATING MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS AFTER THE FAILURE OF CONVENTIONAL THERAPY* (FEBRUARY 2015)

- Infliximab, adalimumab and golimumab are recommended, within their marketing authorisations, as options for treating moderately to severely active ulcerative colitis in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
- The choice of treatment between infliximab, adalimumab or golimumab should be made on an individual basis after discussion between the responsible clinician and the patient about the advantages and disadvantages of the treatments available. This should take into consideration therapeutic need and whether or not the patient is likely to adhere to treatment. If more than 1 treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose).
- Infliximab is recommended, within its marketing authorisation, as an option for treating severely active ulcerative colitis in children and young people aged 6–17 years whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
- Infliximab, adalimumab or golimumab should be given as a planned course of treatment until treatment fails (including the need for surgery) or until 12 months after starting treatment, whichever is shorter. Specialists should then discuss the risks and benefits of continued treatment with the patient, and their parent or carer if appropriate:
- They should continue treatment only if there is clear evidence of response as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. People who continue treatment should be reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate.
- They should consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People whose disease relapses after treatment is stopped should have the option to start treatment again.

PACEF Recommendation:
Infliximab intravenous infusion (*RemicadeInflectralRemsima*) is designated RED for the treatment of moderately to severely active ulcerative colitis in adults and severely active ulcerative colitis in children and young people aged 6–17. Similarly, adalimumab injection (*Humira*) and golimumab injection (*Simponi)* are designated RED for the treatment of moderate to severely active ulcerative colitis in adults All three medicines are approved for inclusion in the *Lincolnshire Joint Formulary* for these indications.

NICE TECHNOLOGY APPRAISAL 332 *SIPULEUCEL-T FOR TREATING ASYMPTOMATIC OR MINIMALLY SYMPTOMATIC METASTATIC HORMONE-RELAPSED PROSTATE CANCER* (FEBRUARY 2015)

Sipuleucel-T is not recommended within its marketing authorisation for treating adults who have asymptomatic or minimally symptomatic metastatic non-visceral hormone-relapsed prostate cancer for which chemotherapy is not yet clinically indicate

Notes
Sipuleucel-T intravenouis infusion (*Provenge*) is an autologous cellular immunotherapy that stimulates the patient's own immune cells to identify and attack prostate cancer cells. Sipuleucel-T has a marketing authorisation in the UK for the treatment of asymptomatic or minimally symptomatic metastatic (non-viscerall) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated. The product has not yet been launched in England.

NICE TECHNOLOGY APPRAISAL 333: *AXITINIB FOR TREATING ADVANCED RENAL CELL CARCINOMA AFTER FAILURE OF PRIOR SYSTEMIC TREATMENT* (FEBRUARY 2015)

- Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme.

PACEF Recommendation
Axitinib 1mg and 5mg tablets (*Inlyta*) are approved for use for the treatment of adult patients with advanced renal cell carcinoma, after failure of prior treatment with sunitinib. They are designated RED and approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.

NICE TECHNOLOGY APPRAISAL 334: *REGORAFENIB FOR METASTATIC COLORECTAL CANCER AFTER TREATMENT FOR METASTATIC DISEASE* (TERMINATED APPRAISAL) (FEBRUARY 2015)

NICE is unable to make a recommendation about the use in the NHS of regorafenib for metastatic colorectal cancer after treatment for metastatic disease because no evidence submission was received from Bayer for the technology. According to the manufacturer, there is currently no evidence base on which to compare regorafenib for metastatic colorectal cancer with standard care in the UK.

PACEF Recommendation:
Regorafenib 40mg tablets (*Stivarga*) are designated RED-RED for this indication. They are not approved for inclusion in the *Lincolnshire Joint Formulary*.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) DRUG SAFETY UPDATE (MARCH 2015)

Dimethyl fumarate (Tecfidera): fatal PML in a multiple sclerosis patient with severe, prolonged lymphopenia

Dimethyl fumarate is licensed to treat relapsing remitting multiple sclerosis in adults. The MHRA have received details of a fatal case of progressive Multifactorial leukoencephalopathy (PML) which was reported in Germany in October 2014 in a patient

participating in the open-label ENDORSE study of dimethyl fumarate in multiple sclerosis. The patient received dimethyl fumarate for 4.5 years and experienced severe lymphopenia for more than 3.5 years.

This is the only known case of PML associated with dimethyl fumarate in a multiple sclerosis patient to date. Cases of PML have been reported with the use of fumaric acid esters (including dimethyl fumarate) in lymphopenic patients with psoriasis. However, in some of these cases, it could not be confirmed that the treatment caused PML (eg other risk factors for PML may have been present).

PACEF Comment
Dimethyl fumarate (Tecfidera) is designated RED and is only prescribed in Lincolnshire under the direct supervision of specialist MS services. Primary care clinicians currently caring for patients with MS who are taking dimethyl fumarate need to be aware of the MHRA advice to healthcare professionals.

MHRA advice to healthcare professionals

During dimethyl fumarate treatment:
- monitor patients - check full blood counts, including lymphocytes, every 6 to 12 months or more frequently if clinically indicated.
- monitor patients with lymphopenia closely for features of PML (e.g. signs and symptoms of neurological dysfunction) and other opportunistic infections.
- stop dimethyl fumarate treatment immediately and investigate appropriately if you suspect PML.
- consider that PML can present with similar features to multiple sclerosis because PML is also a demyelinating disease.

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