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 10; Number 7 **May 2016**

What's new this month?

- ***ZeroAQS*** **cream is approved for use as a first line alternative to aqueous cream for the treatment of flaking dry skin conditions. It is SLS free and lower in cost than alternatives. It is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary* (see page 5).**
- ***Zerobase*** **cream is approved for use as a first line alternative to *Diprobase* cream for the treatment of red, inflamed, dry skin and as a diluent for topical steroids. It is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary* (see page 6).**
- **E45 cream is widely prescribed in Lincolnshire, but is not advocated for use by ULH dermatologists due to its lanolin content; designation GREEN. *ZeroCream* cream is a directly equivalent product at a significantly lower price. It is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*. It should be used first line in preference to *E45* cream (see page 6).**
- ***Zeroderm*** **ointment is approved for use as a first line alternative to *Hydromol Ointment* for the treatment of dry skin in eczema and psoriasis and in other dry skin conditions. It is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary* (see page 7).**
- ***Zerodouble*** **gel is approved for use as a first line alternative to *Doublebase* gel for the treatment of eczema, psoriasis, dermatitis, ichthyosis, elderly pruritus and other dry skin conditions. It is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary* (see page 8).**
- ***Zerolatum Bath Emollient*** **is not recommended for use; designation RED-RED. Prescribers are advised not to initiate any new patients on bath or shower emollients due to lack of evidence of effectiveness and increased risk of slipping and falling in the bath or shower. Preferred alternative strategies include using emollients as soap substitutes or directly applying emollients after bathing (see page 8).**
- **Both *Cetraben* lotion and *Cetraben* ointment are recommended for inclusion in the *Lincolnshire Joint Formulary* for the treatment of dry skin conditions and eczema; both products are designated GREEN (see page 9).**
- **Biosimilar etanercept (*Benepali*) 50mg injection pre-filled syringe and pre-filled pen is approved for use within licensed indications and subject to NICE guidance. It is designated RED and has been approved for inclusion in the *Lincolnshire Joint Formulary* as a lower cost preferred alternative to etanercept 50mg pre-filled syringe/ pre-filled pen (*Enbrel*) (see page 10).**
- **Mexiletine 100mg and 200mg capsules are approved for reinstatement on the *Lincolnshire Joint Formulary* for the treatment of life-threatening ventricular arrhythmias. Designated AMBER without shared care (see page 11).**
- ***Fresubin Thickened Stage 1 and Stage 2 are*** **approved for use within Lincolnshire Hospitals for patients requiring nutritional supplementation to the level of *Fresubin Protein Energy* who are currently experiencing swallowing difficulties. Designation RED, for hospital use only (see page 10).**

- **Tedizolid (*Sivextro*) is approved for use in hospital as an alternative to linezolid in the treatment of acute bacterial skin and skin structure infections in adults. All tedizolid and linezolid preparations are designated RED and should not be prescribed in primary care (see page 12).**
- **Ezetimibe guidance remains unchanged after NICE publish an updated Technology Appraisal on the use of ezetimibe in primary heterozygous-familial and non-familial hypercholesterolaemia (see page 13).**

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SUMMARY OF PACEF DECISIONS: *April 2016 UPDATE*

Device, Dressing or Drug	**Indication(s)**	**Traffic Light and *Joint Formulary* Status**
*Cetraben l*otion (Thornton and Ross)	For the treatment of dry skin conditions and eczema.	GREEN Included in the *Lincolnshire Joint Formulary*.
Cetraben ointment (Thornton and Ross)	For the treatment of dry skin conditions and eczema.	GREEN Included in the *Lincolnshire Joint Formulary*.
E45 cream (Forum)	For ichthyosis, dermatitis, traumatic dermatitis, dry stages of, eczema, dry psoriasis and dry skin conditions.	GREEN Included in the *Lincolnshire Joint Formulary*. *ZeroCream* should be preferred first line.
Etanercept 50mg pre-filled syringe/ pre-filled pens (*Benepali*) (Biogen Idec Ltd)	For use in combination with methotrexate for the treatment of moderate to severe active rheumatoid arthritis in adults when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate. For use as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. For the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate. For the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug therapy has been inadequate. For the treatment of adults with severe active ankylosing spondylitis who have had an inadequate response to conventional therapy. For the *t*reatment of adults with	RED Preferred lower cost alternative to etanercept (*Enbrel*) Approved for inclusion in *Lincolnshire Joint Formulary.*

	severe non-radiographic axial spondyloarthritis who have had an inadequate response to nonsteroidal anti-inflammatory drugs (NSAIDs). For the treatment of adults with moderate to severe plaque psoriasis who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy, including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA) (	
Ezetimibe 10mg tablets(*Ezetrol*) (MSD)	In combination with statins as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia who are not appropriately controlled with a statin alone. Ezetimibe monotherapy is indicated as adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia in whom a statin is considered inappropriate or is not tolerated. To reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin. Co-administered with a statin, ezetimibe is indicated as adjunctive therapy to diet for use in patients with homozygous familial hypercholesterolaemia. Patients may also receive adjunctive treatments (e.g., LDL apheresis). Ezetimibe is indicated as adjunctive therapy to diet for use in patients with homozygous familial sitosterolaemia.	GREEN subject to prescribing guidance. Included in the *Lincolnshire Joint Formulary.*
Fresubin Thickened Stage 1, 200ml bottle (Fresenius-Kabi)	Nutritional supplement for dysphagia or disease-related malnutrition	AMBER subject to assessment by a Speech and Language Therapist or a Dysphagia Trained Nurse. Approved for inclusion in *Lincolnshire Joint Formulary*.
Fresubin Thickened Stage 2, 200ml bottle (Fresenius-Kabi)	Nutritional supplement for dysphagia or disease-related malnutrition	AMBER subject to assessment by a Speech and Language Therapist or a Dysphagia Trained Nurse. Approved for inclusion in *Lincolnshire Joint Formulary*.
Linezolid 600mg tablets (*Zyvox Tablets*) (Pfizer)	For nosocomial pneumonia, community acquired pneumonia and complicated skin and soft tissue infections in a hospital environment	RED Included in the *Lincolnshire Joint Formulary.*
Linezolid oral suspension 100mg in 5ml (*Zyvox Oral Suspension*) (Pfizer)	For nosocomial pneumonia, community acquired pneumonia and complicated skin and soft tissue infections in a hospital environment	RED Included in the *Lincolnshire Joint Formulary.*
Mexiletine 100mg and 200mg capsules	For the treatment of life-threatening ventricular arrhythmias	AMBER without shared care. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Ruxolitinib (*Jakavi*) 5mg,10mg,15mg and 20mg tablets (Novartis Pharmaceuticals Ltd)	For the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis	RED Included in the *Lincolnshire Joint Formulary.*

	(also known as chronic idiopathic myelofibrosis), post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis.	
Simvastatin/ezetimibe (*Inegy*) 20mg/10mg, 40mg/10mg and 80mg/10mg tablets (MSD)	To reduce the risk of cardiovascular events in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS), either previously treated with a statin or not. As adjunctive therapy to diet for use in patients with primary (heterozygous familial and non-familial) hypercholesterolaemia or mixed hyperlipidaemia where use of a combination product is appropriate: (i.e. in patients not appropriately controlled with a statin alone or patients already treated with a statin and ezetimibe) As adjunctive therapy to diet for use in patients with homozygous familial hypercholesterolaemia. Patients may also receive adjunctive treatments (e.g., low-density lipoprotein [LDL] apheresis).	RED-RED Not included in the *Lincolnshire Joint Formulary.*
Tedizolid 200mg powder for solution for infusion (*Sivextro*) (Merck Sharp and Dohme)	For the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.	RED Approved for inclusion in the *Lincolnshire Joint Formulary*.
Tedizolid 200mg tablet (*Sivextro*) (Merck Sharp and Dohme)	For the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults.	RED Approved for inclusion in the *Lincolnshire Joint Formulary*.
Temozolomide (*Temodal*) 5mg, 20mg, 100mg, 140mg, 180mg and 250mg tablets (Merck, Sharp and Dohme Ltd)	For the treatment of adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.	RED Approved for inclusion in the *Lincolnshire Joint Formulary*.
ZeroAQS cream (T&R Derma)	For flaking dry skin conditions.	GREEN first line alternative to Aqueous Cream. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Zerobase cream (T&R Derma)	For the treatment of red, inflamed, dry skin and as a diluent for topical steroids.	GREEN first line alternative to *Diprobase*. Approved for inclusion in the *Lincolnshire Joint Formulary*.
ZeroCream cream (T&R Derma)	For ichthyosis, dermatitis, sunburn, eczema, psoriasis, dry or chapped skin.	GREEN first line alternative to *E45* cream. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Zeroderm ointment (T&R Derma)	For the treatment of dry skin in eczema and psoriasis and in other dry skin conditions.	GREEN first line alternative to *Hydromol Ointment*. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Zerodouble gel (T&R Derma)	For the treatment of eczema, psoriasis, dermatitis, ichthyosis, elderly pruritus and other dry skin conditions	GREEN first line alternative to *Doublebase gel*. Approved for inclusion in the *Lincolnshire Joint Formulary*.
Zerolatum Bath Emollient (T&R Derma)	For dermatitis, senile pruritis, ichthyosis and related dry skin disorders.	RED-RED Not approved for inclusion in the *Lincolnshire 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 PACEF website (http://lincolnshire-pacef.nhs.uk). 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

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

RAPID DRUG ASSESSMENT: *NEW ZERODERMA RANGE OF EMOLLIENTS*

The new Zeroderma range of emollients offer lower cost alternatives to well established first line products; *ZeroAQS* cream, *Zerobase* cream, *ZeroCream* cream, *Zeroderm* ointment and *Zerodouble* gel have all been approved for use.

Thornton and Ross Derma have recently launched as range of lower cost emollients. PACEF have reviewed each product in the range in comparison to equivalent products already on the *Lincolnshire Joint Formulary*.

ZeroAQS cream

ZeroAQS cream is indicated for flaking dry skin conditions. The table below compares the content of *ZeroAQS* cream to alternative *Formulary* emollients:

Ingredients	***ZeroAQS* cream**	**Aqueous cream**	***Aquamax* cream**
Emollient	Liquid paraffin 6%; white soft paraffin 15%	Liquid paraffin 6%; white petroleum jelly 15%	Liquid paraffin 8%; white soft paraffin 20%
Emulsifier	Macrogol cetostearyl ether Cetostearyl alcohol	Cetostearyl alcohol	cetostearyl alcohol, Poly-sorbate 60
Preservative	chlorocresol	phenoxy-ethanol	phenoxy-ethanol
Water based cream	purified water 69.8%	purified water 69%	purified water
SLS free	√	X	√

Neither *ZeroAQS* cream nor *Aquamax* cream contain sodium lauryl sulphate (SLS) which can cause skin irritation. The MHRA have advised that, where skin irritation is associated with the use of aqueous cream, an alternative SLS free emollient should be prescribed. ULH dermatologists and PACEF recommend that, where possible, SLS free emollients should be preferred. A cost comparison reveals that *ZeroAQS* cream is the lowest price SLS free, aqueous cream alternative.

Drug	**Cost (£)**	**Cost per g**
ZeroAQS cream (T&R Derma)	£3.29 500g	0.7p
Aqueous cream	£0.95 100g	0.95p

	£4.75 500g	0.95p
Aquamax Cream (Dermato Logical)	£1.89; 100g £3.99 500g	1.9p 0.8p

The potential saving across Lincolnshire if *ZeroAQS* cream was used instead of aqueous cream or *Aquamax* cream would be £11,266pa.

PACEF Recommendation:
***ZeroAQS* cream is approved for use as a first line alternative to aqueous cream for the treatment of flaking dry skin conditions. It is SLS free and lower in cost than alternatives such as Aqueous cream. It is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*.**

Zerobase cream

Zerobase cream is indicated for the treatment of red, inflamed, dry skin and as a diluent for topical steroids. It is closely comparable to *Diprobase* cream (see table below) at a lower cost (see cost comparison).

Ingredients	Zerobase cream	Diprobase cream
Emollient	Liquid paraffin 11% White soft paraffin 10%	Liquid paraffin 6% White soft paraffin 15%
Emulsifier	Cetomacrogol Cetostearyl alcohol	Cetomacrogol Cetostearyl alcohol
Preservative	chlorocresol	chlorocresol
Ph modification acid	Phosphoric acid	Phosphoric acid
Ph modification alkaline	Sodium dihydrogen phosphate	Sodium dihydrogen phosphate Sodium hydroxide

Cream	Cost (£)	Cost per g
Zerobase cream (T&R Derma)	£1.04 50g £5.26 500g pump dispenser	2p 1p
Diprobase cream (Bayer Consumer)	£1.28 50g £6.32 500g with dispenser	2.6p 1.26p

The potential saving across Lincolnshire if *Zerobase* cream were used instead of *Diprobase* cream would be £22,016 pa.

PACEF Recommendation:
***Zerobase* cream is approved for use as a first line alternative to *Diprobase* cream for the treatment of red, inflamed, dry skin and as a diluent for topical steroids. It is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*.**

ZeroCream cream

ZeroCream cream is indicated for ichthyosis, dermatitis, sunburn, eczema, psoriasis, dry or chapped skin. It is the competitor product in the T & R Derma range to *E45* cream. A comparison reveals the following:

Ingredients	*ZeroCream* cream	*E45* cream
Emollient	Liquid paraffin 12.6% White soft paraffin 14.5%	Liquid paraffin 12.6% White soft paraffin 14.5%

	Anhydrous lanolin 1%	Anhydrous lanolin 1%
Emulsifier	Glyceryl monostearate Sodium cetostearyl sulphate	Glyceryl monostearate Sodium cetostearyl sulphate
Preservative	Hydroxybenzoates 2-phenoxyethanol	Hydrobenzoates
Ph modification	Citric acid monohydrate	Citric acid monohydrate
Ph modification alkaline	Sodium hydroxide	Sodium hydroxide
Thickener	Carbomer	Carbomer
Water based cream	Purified water	Purified water

Cream	**Cost (£)**	**Cost per g**
ZeroCream **cream** (T&R Derma)	£1.17 50g £4.08 500g pump dispenser	2.3p 0.8p
E45 **cream** (Forum)	£1.61 50g £2.91 125g £5.17 350g £5.62 500g with dispenser	3.2p 2.3p 1.5p 1.1p

The potential savings across Lincolnshire if *ZeroCream* is used instead of *E45* cream would be £26,095pa.

PACEF Recommendation:
E45 **cream is widely prescribed in Lincolnshire, but is not advocated for use by ULH dermatologists due to its lanolin content; designation GREEN.** ***ZeroCream*** **cream is a directly equivalent product at a significantly lower price. It is designated GREEN and approved for inclusion in the** ***Lincolnshire Joint Formulary*****. It should be used first line in preference to E45 cream.**

Zeroderm ointment

Zeroderm ointment is indicated for the treatment of dry skin in eczema and psoriasis and in other dry skin conditions. It is the equivalent product in the T&R Derma range to *Hydromol* ointment. Although *Hydromol* ointment is currently listed on the *Joint Lincolnshire Formulary*, it is not currently prescribed. A comparison of the two products reveals the following:

Ingredients	***Zeroderm*** **ointment**	***Hydromol*** **ointment**
Emollients	Liquid paraffin 40% White soft paraffin 30%	Liquid paraffin 40% White soft paraffin 30%
Emulsifier	Cetearyl alcohol Polysorbate 60	Cetomacrogol emulsifying wax
SLS free	√	√

Drug	**Ingredients**	**Cost (£)**	**Cost per g**
Zeroderm ointment (T&R Derma)	Liquid paraffin 40%, white soft paraffin 30%	£2.41 125g £4.10 500g	2p 0.9p
Hydromol Ointment (Alliance)	**YSP 30%, emulsifying wax 30%, liquid paraffin 40%)**	**£2.88 125g** **£4.89 500g** **£9.09 1kg**	**2.3p** **1p** **0.9p**

PACEF Recommendation:
***Zeroderm* ointment is approved for use as a first line alternative to *Hydromol Ointment* for the treatment of dry skin in eczema and psoriasis and in other dry skin conditions. It is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*.**

Zerodouble gel

Zerodouble gel is indicated for the treatment of eczema, psoriasis, dermatitis, ichthyosis, elderly pruritus and other dry skin conditions and is a directly equivalent lower cost alternative to *Doublebase* gel:

Ingredients	*Zerodouble* gel	*Doublebase* gel
Emollients	Isopropyl myristate 15% Liquid paraffin 15%	Isopropyl myristate 15% Liquid paraffin 15%
Preservative	phenoxyethanol	phenoxyethanol
Humectant	Glycerin	Glycerol
Emulsifier	acrylates	carbomer
Emulsifier/ surface wetting agent	Sorbitan laurate	Sorbitan laurate
PH modifier	triethanolamine	triethanolamine
Water base	Purified water	Purified water
Common sensitizers & irritants	None	None

Drug	**Ingredients**	**Cost (£)**	**Cost per g**
***Zerodouble* gel (T&R Derma)**	Liquid paraffin 15%, isopropyl myristate 15%	£2.25 100g £4.71 475g	2.25p 0.99
***Doublebase* gel (Dermal)**	Isopropyl myristate 15%, liquid paraffin 15%	£2.65 100g £5.83 500g pump dispenser	2.65p 1.2p

The potential savings across Lincolnshire if *Zerodouble* gel were used instead of *Doublebase gel* would be £10,009pa.

PACEF Recommendation:
***Zerodouble gel* is approved for use as a first line alternative to *Doublebase gel* for the treatment of eczema, psoriasis, dermatitis, ichthyosis, elderly pruritus and other dry skin conditions. It is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*.**

Potential CCG savings (assuming 100% switch)

Switch	**LECCG**	**LWCCG**	**SLCCG**	**SWLCCG**
Aqueous cream to *ZeroAQS* cream	£4,532	£2,617	£2,127	£1,990
Diprobase cream to *Zerobase* cream	£5,436	£7,530	£4,868	£4,182
E45 cream to *Zerocream* cream	£11,279	£5,415	£6,191	£3,210
Doublebase gel to *Zerodouble* gel	£2,977	£2,737	£2,352	£1,943
Total	£24,224	£18,299	£15,538	£11,325

Zerolatum and alternative bath emollients

In addition to the range of products listed above, T&R Derma have also launched *Zerolatum Bath Emollient* as an alternative to established bath emollients such as *Balneum* bath oil, *E45 Bath Oil*, *Hydromol Bath and Shower* and *Oilatum Emollient.*

The ULH Dermatology Service advise that emollient bath additives should no longer be used as part of standard total emollient therapy. The amount of emollient deposited on the skin during bathing or showering using a bath or shower emollient is likely to be far lower than that deposited from directly applied emollients *after* bathing or showering.

The *Drug and Therapeutic Bulletin* (*DTB*) reviewed the use of bath emollients in the management of eczema in 2007. The review identified a lack of published randomised controlled trials supporting the use of bath emollients in the treatment of atopic eczema and emphasized the lack of consensus of clinical opinion that such therapy is effective. *DTB* concluded that alternative strategies focused on using emollients as soap substitutes or directly applying emollients after bathing were preferable and potentially more effective.

The *British Medical Journal* (*BMJ*) also published an article in 2009 questioning the role of bath emollients. Again, the lack of published evidence was highlighted as a problem. The article also pointed out that the quantity of emollient deposited on the skin from a bath emollient whilst bathing is likely to be far lower than that achieved with directly applied emollients. The authors conclude that, based on current evidence, bath emollients offer little or no benefit and that over-reliance on these products could lead to substandard emollient therapy.

In addition, bath and shower emollients coat the surface of the bath and shower creating a very greasy and slippery surface; this can markedly increase the risk of slipping and falling, particularly in children and the elderly.

The current annual spend on bath and shower emollients across all four Lincolnshire CCGs is £137,463pa. In terms of volume, bath and shower emollients account for approximately a quarter to a third of all emollients prescribed.

PACEF Recommendation:
***Zerolatum Bath Emollient* is not recommended for use; designation RED-RED and is not approved for inclusion in the *Lincolnshire Joint Formulary.* Prescribers are advised not to initiate any new patients on bath or shower emollients due to lack of evidence of effectiveness and increased risk of slipping and falling in the bath or shower. Preferred alternative strategies include using emollients as soap substitutes or directly applying emollients after bathing.**

RAPID COST COMPARISON: *CETRABAN OINTMENT AND LOTION*

***Cetraben* lotion and *Cetraben* ointment are recommended for inclusion in the *Lincolnshire Joint Formulary* for the treatment of dry skin conditions and eczema**

Cetraben lotion and *Cetraben* ointment are indicated for the treatment of dry skin conditions and eczema. A rapid review of comparative costs against alternative *Formulary* approved products (such as *Aveeno* lotion, *Dermol* lotion, *Diprobase* ointment, *Hydromol* ointment and *Zeroderm* ointment) has resulted in PACEF approving both products for inclusion in the *Lincolnshire Joint Formulary*. *Cetraben* ointment may be preferable to alternative yellow soft paraffin containing products (such as *Hydromol* ointment) as there is a reduced potential to stain bedding and clothing.

PACEF Recommendation
Both *Cetraben* lotion and *Cetraben* ointment are recommended for inclusion in the *Lincolnshire Joint Formulary* for the treatment of dry skin conditions and eczema; both products are designated GREEN.

NEW DRUG ASSESSMENT: *ETANERCEPT 50MG SB4 – BIOSIMILAR (BENPALI)*

Biosimilar etanercept (*Benepali*) 50mg injection is approved for use within licensed indications and subject to NICE guidance as a lower cost alternative to *Enbrel.*

Etanercept, in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and psoriasis in adults when the response to previous disease modifying anti-rheumatic drugs has been inadequate. Etanercept can also be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Current NICE guidance supports a role for the product in the treatment of rheumatoid arthritis, severe active ankylosing spondylitis and active and progressive psoriatic arthritis. Until recently, the only etanercept preparation available in the UK was etanercept (*Enbrel*) powder and solvent for solution 10mg, 25mg and 50mg vials, pre-filled syringes and pre-filled pens. In line with NICE guidance, this product is approved for use through the *Lincolnshire Joint Formulary* designation RED.

A new biosimilar formulation of etanercept, *Benepali* 50mg solution for injection, was launched in the UK in February 2016, available as both a pre-filled syringe and a pre-filled pen. It is also licensed for the treatment of active psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis and plaque psoriasis in adults when the response to previous conventional therapy has been inadequate.

In a multi-centre, randomised, double-blind, parallel group trial in 596 adults with moderate to severe rheumatoid arthritis, biosimilar etanercept (SB4) 50mg once weekly was compared with standard etanercept 50mg once weekly over 52 weeks. At the completion of the trial, biosimilar etanercept was found to be equivalent in terms of clinical efficacy and tolerability to standard etanercept. A cost comparison of *Benepali* and *Enbrel* using secondary care and Homecare costs reveals that *Benepali* costs nearly £60 per patient per week less than *Enbrel:*

Drug	Dose	Homecare Cost per dose
Etanercept 50mg pre-filled syringe/ pre-filled pens (*Benepali*) (Biogen Idec Ltd)	50mg once weekly by subcutaneous injection	£120.00
Etanercept 50mg pre-filled syringe/ pre-filled pen (*Enbrel*) (Pfizer)	50mg once weekly by subcutaneous injection	£178.75

PACEF Recommendation;
Biosimilar etanercept (*Benepali*) 50mg injection pre-filled syringe and pre-filled pen is approved for use within licensed indications and subject to NICE guidance. It is designated RED and has been approved for use through the *Lincolnshire Joint Formulary* as a lower cost preferred alternative to etanercept 50mg pre-filled syringe/ pre-filled pen (*Enbrel*).

RAPID DRUG ASSESSMENT: *MEXILETINE 100MG AND 200MG CAPSULES (MEXITIL)*

Mexiletine 100mg and 200mg capsules are approved for reinstatement on the *Lincolnshire Joint Formulary* for the treatment of life-threatening ventricular arrhythmias and designated AMBER without shared care.

Mexiletine is a class Ib antiarrhythmic with actions similar to those of lidocaine. Unlike lidocaine, mexiletine undergoes little hepatic first-pass metabolism and can be taken orally. It is used for the treatment of life-threatening ventricular arrhythmias.

Current European Society of Cardiology *Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death* (2015) state the following:

> 'it has been demonstrated that some sodium current blockers (predominantly class Ib agents like mexiletine and class Ic like flecainide) actively inhibit both the peak sodium current and the late component of the sodium current. In doing so, these agents may induce an abbreviation of the QT interval in patients with LQTS type 3… Combinations of sodium channel blockers and potassium channel blockers (e.g. mexiletine and sotalol, or amiodarone and flecainide/propafenone) have been used, usually in patients with frequent VT recurrences who have a defibrillator.'

Mexiletine capsules were discontinued in the UK in June 2008 due to low demand. Since then, they have been available solely from 'special order' manufacturers or specialist importing companies.

ULH Cardiology have recently requested that mexiletine 100mg and 200mg capsules should be reinstated onto the *Lincolnshire Joint Formulary* for the treatment for potentially life threatening ventricular arrhythmias. 1 months' treatment at a dose of 200mg three times a day will cost approximately £318.13 per patient.

PACEF Recommendation:
PACEF acknowledge the re-emergence of mexiletine in the treatment of life-threatening ventricular arrhythmias and the potential for an expanding role if predicted supply difficulties with amiodarone and flecainide materialise later in the year (see *PACE Bulletin* Volume 10 No 6 (May 2016)). As a result of this, mexiletine 100mg and 200mg capsules are designated AMBER without shared care. Mexiletine is approved for inclusion in the *Lincolnshire Joint Formulary* for the treatment of life-threatening ventricular arrhythmias.

RAPID PRODUCT ASSESSMENT: *FRESUBIN THICKENED STAGE 1 AND STAGE 2*

***Fresubin Thickened Stage 1 and Stage 2 are* approved for use within Lincolnshire Hospitals for patients requiring nutritional supplementation to the level of *Fresubin Protein Energy* who are currently experiencing swallowing difficulties.**

Fresubin Thickened Stage 1 and *Stage 2* are high protein, high energy (1.5kcal/ml) nutritional supplements equivalent in energy and protein content to *Fresubin Protein Energy* (see below). *Fresubin Thickened* is available in two consistencies, syrup (*Stage 1*) and custard (*Stage 2*), and two flavours, vanilla and wild strawberry. These products have been developed for those with dysphagia who are suffering from disease related malnutrition.

A cost comparison reveals that the thickened products are marginally more expensive than the non-thickened product in primary care; in secondary care the products are comparably priced.

Product name	Protein content	Energy content	Flavours	Cost and Pack Size	Cost per kcal	Comments
Fresubin Protein Energy (Fresenius Kabi)	20g	300kcal 1.5kcal/ml	Vanilla, Chocolate, Tropical Fruits, Cappuchino, Wild Strawberry	£2.10 per 200ml bottle	0.7p	Lactose Free Gluten Free Not nutritionally complete
Fresubin Thickened Stage 1 (Fresenius Kabi)	20g	300kcal 1.5kcal/ml	Vanilla Wild Strawberry	£2.28 per 200ml bottle	0.8p	Syrup consistency Gluten-free Lactose-free Not nutritionally complete
Fresubin Thickened Stage 2 (Fresenius Kabi)	20g	300kcal 1.5kcal/ml	Vanilla Wild Strawberry	£2.28 per 200ml bottle	0.8p	Custard consistency Gluten-free Lactose-free Not nutritionally complete

Definitions

Stage 1 (syrup)	**Stage 2 (custard)**
Can be drunk through a straw.	Cannot be drunk through a straw.
Can be drunk from a cup if preferred.	Can be drunk from a cup.
Leaves a thin coat on the back of a spoon.	Leaves a thick coat on the back of a spoon.

PACEF Recommendation

***Fresubin Thickened Stage 1 and Stage 2 are* approved for use for patients requiring nutritional support to the level of *Fresubin Protein Energy* who are currently experiencing swallowing difficulties. These products should only be prescribed following an assessment by a Speech and Language Therapist or a Dysphagia Trained Nurse. Subject to appropriate assessment, they are designated AMBER and approved for use through the *Lincolnshire Joint Formulary*.**

NEW DRUG ASSESSMENT: *TEDIZOLID 200MG TABLETS AND 200MG POWDER FOR SOLUTION FOR INFUSION (SIVEXTRO)*

Tedizolid (*Sivextro*) is approved for use in hospital as an alternative to linezolid in the treatment of acute bacterial skin and skin structure infections in adults.

Tedizolid is licensed for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. It is bacteriostatic against enterococci, staphylococci, and streptococci in vitro and is primarily active against Gram-positive bacteria.

Two double-blind, randomised controlled studies; ESTABLISH-1 and ESTABLISH-2 compared tedizolid phosphate with linezolid in patients with ABSSSI. Results showed non inferiority compared to linezolid with primary outcomes measured as early clinical response at the 48 to 72 hour assessment. Either tedizolid tablets or infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to oral when clinically indicated.

Tedizolid emerges from trials as non-inferior to linezolid and has fewer contra-indications and interactions. It is comparably priced to linezolid in primary care; in secondary care tedizolid is significantly more expensive than linezolid.

	Dose	**Cost**
Tedizolid 200mg tablet (*Sivextro*) (Merck Sharp and Dohme)	200mg once daily for 6 days	£862.00
Linezolid 600mg tablets	600mg every 12 hours for 10 days	£890.00
Linezolid oral suspension 100mg in 5ml	600mg every 12 hours for 10 days	£890.00

*prices quoted for linezolid are for 10 days; the SPC defines a treatment course of 10-14 days.

PACEF Recommendation:
Tedizolid 200mg tablets and powder for solution for infusion (Sivextro) are designated RED for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults. Both formulations are approved for inclusion in the *Lincolnshire Joint Formulary*. Under no circumstances should tedizolid or linezolid be prescribed in primary care.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 385: *EZETIMIBE FOR TREATING PRIMARY HETEROZYGOUS-FAMILIAL AND NON-FAMILIAL HYPERCHOLESTEROLAEMIA* (FEBRUARY 2016)

- Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults for whom initial statin therapy is contra-indicated.
- Ezetimibe monotherapy is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who cannot tolerate statin therapy.
- Ezetimibe, co-administered with initial statin therapy, is recommended as an option for treating primary (heterozygous-familial or non-familial) hypercholesterolaemia in adults who have started statin therapy when: (1) **serum total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) concentration is not appropriately controlled** either after appropriate dose titration of initial statin therapy or because dose titration is limited by intolerance to initial statin therapy or (2) **consideration is being given to changing from initial statin therapy to an alternative statin.**
- When prescribing ezetimibe co-administered with a statin, ezetimibe should be prescribed on the basis of lowest acquisition cost.
- Intolerance to initial statin therapy should be defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.
- Appropriate control of cholesterol concentrations should be based on individualised risk assessment in accordance with national guidance on the management of cardiovascular disease in the relevant populations.

Percentage Reductions in LDL Cholesterol and Total Cholesterol

Statin	Daily Dose	28 day cost	Percentage reduction in LDL-C	Percentage reduction in total cholesterol
Atorvastatin	**10mg**	**£1.03**	**35-39%**	**32%**
Atorvastatin	**20mg**	**£1.21**	**43%**	**36%**
Atorvastatin	**40mg**	**£1.39**	**50%**	**42%**

Atorvastatin	**80mg**	**£2.41**	**55-60%**	**47%**
Pravastatin	10mg	£1.02	22%	14.7%
Pravastatin	20mg	£1.23	32%	17.2%
Pravastatin	40mg	£1.60	34%	29%
Rosuvastatin (*Crestor*)	5mg	£18.03	45%	33%
Rosuvastatin (*Crestor*)	10mg	£18.03	46-52%	36%
Rosuvastatin (*Crestor*)	20mg	£26.02	47-55%	40%
Rosuvastatin (*Crestor*)	40mg	£29.69	55-63%	46%
Simvastatin	10mg	£0.74	30%	20.3%
Simvastatin	20mg	£0.85	38%	25.7%
Simvastatin	40mg	£0.94	42%	29%
Simvastatin	80mg	£1.61	46%	32%
Ezetimibe (*Ezetrol*) (MSD)	10mg	£26.21	20%	14%
Simvastatin/ezetimibe (*Inegy*) (MSD)	20mg/10mg	£33.42	52%	37%
Simvastatin/ezetimibe (*Inegy*) (MSD)	40mg/10mg	£38.98	55%	39%
Simvastatin/ezetimibe (*Inegy*) (MSD)	80mg/10mg	£41.21	60%	43%

PACEF Recommendations:

- **NICE guidance on the role of ezetimibe remains largely unchanged since the last published NICE TA in 2007 with the product retaining a marginal role. Some definitions of heterozygous and homozygous familial hyper-cholesterolaemia appear below.**
- **The cost and effectiveness comparison table above confirms that ezetimibe is less effective in terms of LDL-C and Total Cholesterol than even the lowest potency statin. Statin therapy, even high-cost, high-potency branded statin therapy, should always be preferred to ezetimibe alone unless genuine intolerance to all statins is an unavoidable problem.**
- **Where ezetimibe is prescribed in combination with a statin, separate components should always be preferred as the simvastatin/ezetimibe combination product *Inegy* is prohibitively expensive. Prescribers are reminded that Inegy is a RED-RED product and is not included in the *Lincolnshire Joint Formulary*.**
- **Since February the marketing authorisation for ezetimibe (*Ezetrol*) has been extended to include reduction of 'the risk of cardiovascular events in patients with coronary heart disease and a history of acute coronary syndrome when added to ongoing statin therapy or initiated concomitantly with a statin'.**
- **IMPROVE-IT provides important outcomes based evidence that supports the use of ezetimibe to further reduce LDL-C in secondary prevention of CVD in patients requiring high-intensity statin therapy post ACS who cannot achieve sufficient LDL-C reduction with statins alone or in those intolerant to statin therapy or higher dose statin therapy.**

- **In response to IMPROVE-It, the following changes to Lincolnshire lipid modification guidance were agreed with local cardiologists: First line statin therapy post ACS remains atorvastatin 80mg; high intensity atorvastatin therapy as advocated by NICE in the secondary prevention of CVD remains the preferred option. Patients who fail to achieve a 40% reduction in non-HDL C using maximum tolerated doses of atorvastatin (or an alternative statin) should be considered for concomitant ezetimibe. Patients who fail to tolerate higher doses of atorvastatin (or an alternative statin) should be down titrated and those not at target initiated on ezetimibe. Patients genuinely statin intolerant (after re-challenge and change of statin) should be considered for ezetimibe. Ezetimibe monotherapy should not be used as a replacement for statin therapy in the majority of patients.**
- **It must be emphasized that local policy in relation to the prescribing of ezetimibe has only been changed for patients requiring high intensity statin therapy post ACS.**
- **Patent protection of the ezetimibe molecule has been extended to October 2017 across Europe; the patent life for the ezetimibe-simvastatin combination product (*Inegy*) is even longer, terminating in April 2019. This means that issues around cost-effectiveness of ezetimibe, particularly within a primary prevention context, are likely to persist for at least another 2 years.**

Definitions

Familial hypercholesterolemia (FH) is a genetic disorder characterized by high cholesterol levels, specifically very high levels of low-density lipoprotein (LDL-C) and total cholesterol, in the blood and early cardiovascular disease. High cholesterol levels in individuals with FH are usually less responsive to dietary modification and statins than high cholesterol levels in those without FH. Nevertheless, treatment with statins, often at higher doses, is usually effective. The condition greatly increases the risk of atherosclerosis, which can lead to heart attacks, strokes and other vascular conditions.

In **heterozygous familial hypercholesterolemia (HeFH),** an individual inherits a mutation for FH from one (affected) parent. In **homozygous familial hypercholesterolemia (HoFH),** an individual inherits a causal FH mutation from both parents.

HeFH is one of the most common genetic diseases and affects at least 1 in 500 individuals. This may be an underestimate as recent genetic studies indicate that FH may be as common as 1 in 250 in European Caucasian populations. Individuals with HeFH have a 20-fold increased risk for coronary heart disease (CHD). Untreated men have a 50% risk of a nonfatal or fatal coronary event by age 50 years; untreated women have a 30% risk by age 60 years. If one or more other risk factors for CHD are present, especially cigarette smoking or diabetes mellitus, the risk of developing symptomatic CHD is even higher. HeFH is treatable and the associated cardiovascular disease is largely preventable with early and intensive treatment, using statins, additional drugs, and other means. Family members of an affected individual found through "cascade screening" or "family tracing" who have not yet exhibited symptoms and who are appropriately treated are likely to live a normal lifespan.

HoFH is very rare (~ 1 in 250,000 to 1 in 1 million). LDL-C levels are usually, though not always, > 400 mg/dl. Severe vascular disease including CHD and aortic stenosis are often seen by the teenage years. Without very aggressive treatment including LDL-C apheresis and HoFH specific medications, mortality is common before age 30.

HeFH is normally treated with statins, bile acid sequestrants, or other lipid lowering agents that lower cholesterol levels. New cases are generally offered genetic counseling. HoFH often does not respond to medical therapy and may require other treatments, including LDL apheresis (removal of LDL in a method similar to dialysis) and occasionally liver transplantation.

NICE Technology Appraisal	Guidance	PACEF Recommendation
TA386 Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis (March 2016)	Ruxolitinib is recommended as an option for treating disease-related splenomegaly or symptoms in adults with primary myelofibrosis (also known as chronic idiopathic myelofibrosis)	Ruxolitinib (*Jakavi*) 5mg,10mg,15mg and 20mg tablets are designated RED for this indication and approved for use through the *Lincolnshire Joint Formulary*.

TA23 Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (March 2016)	Temozolomide is recommended as an option for treating malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy only if the person has a Karnofsky performance status score greater than or equal to 70 and a life expectancy of 12 weeks or more.	Temozolomide (*Temodal*) 5mg, 20mg, 100mg, 140mg, 180mg and 250mg tablets are designated RED for this indication and approved for use through the *Lincolnshire Joint Formulary.*

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