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 9 **June 2015**

What's new this month?

- **Despite a lack of compelling evidence and poor cost-effectiveness, health food supplements containing lutein and antioxidant vitamins such as *Icaps* (various formulations), *Macushield* (various formulations), *Preservision Original and Preservision Lutein* continue to be prescribed on the NHS for the prevention of age-related macular degeneration. Patients concerned about macular degeneration wishing to supplement their dietary intake of these vitamins and minerals should be advised to purchase their own supplies from a community pharmacy, healthfood store or reputable on-line retailer (see page 3).**
- **Information is provided on sourcing lower cost branded products. In an appendix to this *Bulletin*, a table is provided summarizing for each proposed switch: the manufacturer of each product with contact details, the wholesalers who supply each product and confirmation of stock availability. It is strongly recommended that practices considering a switch to a lower cost brand should inform their local community pharmacy or pharmacies of their intention to do so in advance of issuing prescriptions (see page 6 and appendix on page 16).**
- **In view of safety concerns over high-dose fixed combination insulin preparations and the high cost of insulin analogues in comparison to conventional insulins, insulin degludec 100 iu/liraglutide 3.6mg injection (*Xultophy*) is designated RED-RED and is not approved for inclusion in the *Lincolnshire Joint Formulary* (see page 6).**
- **Teva UK have discontinued their brand of morphine sulfate sustained release tablets (*Filnarine SR*). Both *Morphgesic SR* tablets and *Zomorph* sustained release capsules remain available at a significantly lower price than *MST Continus* tablets (see page 8).**
- ***Creon 40,000* capsules (pancreatin) are currently unavailable. Supply of *Creon 25,000* and *Creon 10,000* remains unaffected and prescribers are advised to transfer patients over to the lower strength formulations. In order to minimize the tablet burden, prescribers are advised to transfer to *Creon 25,000*, where possible (see page 9).**
- **NICE have approved empagliflozin (*Jardiance*) for use in combination with other agents for the treatment of type 2 diabetes. Following a review of all three SGLT2 inhibitors, PACEF have concluded that empagliflozin and dapagliflozin (*Forxiga*) are preferred as the first-line SGLT2 inhibitors of choice (see page 10).**
- **Rifaximin tablets 550mg *(Targaxan)* for the reduction in recurrence of overt hepatic encephalopathy have been approved for use by NICE. The product is already available for this indication through the *Lincolnshire Joint Formulary*. Designation: AMBER (see page 11).**
- **Rifaximin tablets 200mg *(Xifaxanta)* are not recommended for non-invasive traveller's diarrhoea. Designation RED-RED and not included in the *Lincolnshire Joint Formulary* for this indication (see page 11).**
- **Hydroxyzine is associated with a small risk of QT interval prolongation and Torsade de Pointes. Such events are most likely to occur in patients who already have risk factors for QT prolongation, such as: (1) concomitant use of medicines that prolong the QT interval; (2) cardiovascular disease; (3) family history of sudden cardiac death; (4) significant electrolyte imbalance (low potassium or magnesium levels) and (5) significant bradycardia. The MHRA have published advice for healthcare professionals (see page 12).**
- **When prescribing or dispensing codeine-containing medicines for coughs and colds, remember that codeine is contraindicated in: children younger than 12 years old;**

patients of any age known to be CYP2D6 ultra-rapid metabolisers and breastfeeding mothers. Codeine is also not recommended for adolescents (12 to 18) who have problems with breathing (see page 12).

- **The MHRA have issued guidance designed to minimize the risk of error resulting from the expanding range of high strength, fixed combination and biosimilar insulin products (see page 13).**

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SUMMARY OF PACEF DECISIONS: *MAY 2015 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Empagliflozin tablets 10mg and 25mg (*Jardiance*) (Boehringer Ingelheim)	For type 2 diabetes inadequately controlled by diet and exercise in combination with other hypo-glycaemics.	GREEN. Included in the *Lincolnshire Joint Formulary.*
Empagliflozin tablets 10mg and 25mg (*Jardiance*) (Boehringer Ingelheim)	For use as monotherapy for the treatment of type 2 diabetes inadequately controlled by diet and exercise when metformin is not tolerated.	RED-RED. Not approved for use through the *Lincolnshire Joint Formulary* for this indication.
Glycopyrronium bromide 2% roll on applicator (unlicensed special)	For the treatment of palmar hyperhidrosis that has failed to respond to oral therapy and iontophoresis.	AMBER without shared care (single patient request)
Icaps – various *Eye Vitamin* formulations including *Lutein and Omega-3 Formula*, *AREDS Formula*, *Multivitamin Formula* and *Lutein and Zeaxanthin Formula* (Alcon)	Health food supplements marketed as aids to the improvement of eye health	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*. Should not be prescribed on the NHS for the prevention of age-related macular degeneration.
Insulin degludec 100 iu/liraglutide 3.6mg injection (*Xultophy*) (Novo Nordisk)	For the treatment of adults with type 2 diabetes to improve glycaemic control in combination with oral glucose lowering medicines when these alone or combined with basal insulin do not provide adequate glycaemic control.	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*.
Macushield Lutein, Zeaxanthin and Meso-zeaxanthin Capsules and *MacuShield Gold Capsules* (Macuvision)	Health food supplements marketed as aids to the improvement of eye health	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*. Should not be prescribed on the NHS for the prevention of age-related macular degeneration.

Occuvite Complete Capsules (Bausch and Lomb)	Health food supplements marketed as aids to the improvement of eye health	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*. Should not be prescribed on the NHS for the prevention of age-related macular degeneration.
Preservision Eye Vitamin and Mineral Food Supplement capsules (Original) (Bausch and Lomb)	Health food supplements marketed as aids to the improvement of eye health	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*. Should not be prescribed on the NHS for the prevention of age-related macular degeneration.
Preservision Eye Vitamin and Mineral Food Supplement capsules (Lutein) (Bausch and Lomb)	Health food supplements marketed as aids to the improvement of eye health	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*. Should not be prescribed on the NHS for the prevention of age-related macular degeneration.
Rifaximin tablets 550mg (Targaxan) (Norgine)	For the reduction in recurrence of overt hepatic encephalopathy	AMBER Included in the *Lincolnshire Joint Formulary* for this indication
Rifaximin tablets 200mg (Xifaxanta) (Norgine)	For non-invasive traveller's diarrhoea	RED-RED Not approved for the *Lincolnshire Joint Formulary* for this indication
Viteyes AREDS 2 Advanced Antioxidant Vitamins plus Zinc, Lutein and Zeaxanthin capsules (Vitamin Health)	Health food supplements marketed as aids to the improvement of eye health	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*. Should not be prescribed on the NHS for the prevention of age-related macular degeneration.
Viteyes 2 plus Omega-3 Softgels (Vitamin Health)	Health food supplements marketed as aids to the improvement of eye health	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*. Should not be prescribed on the NHS for the prevention of age-related macular degeneration.
Visionace Original tablets (Vitabiotics)	Health food supplements marketed as aids to the improvement of eye health	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*. Should not be prescribed on the NHS for the prevention of age-related macular degeneration.
Visionace Plus Omega 3 tablets (Vitabiotics)	Health food supplements marketed as aids to the improvement of eye health	RED-RED not approved for inclusion in the *Lincolnshire Joint Formulary*. Should not be prescribed on the NHS for the prevention of age-related macular degeneration.

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

QIPP OPPORTUNITY: *LUTEIN AND ANTIOXIDANT VITAMINS FOR THE PREVENTION OF AGE-RELATED MACULAR DEGENERATION*

Despite a lack of compelling evidence and poor cost-effectiveness, health food supplements containing lutein and antioxidant vitamins such as *Icaps* (various formulations), *Macushield*, *Preservision Original and Preservision Lutein* continue to be prescribed on the NHS for the prevention of age-related macular degeneration. Patients concerned about macular degeneration wishing to supplement their dietary intake of these vitamins and minerals should be advised to purchase their own supplies from a community pharmacy, healthfood store or reputable on-line retailer.

Background

The exact cause of age-related macular degeneration (AMD) is unknown. Modifiable risk factors include smoking (which more than doubles the risk of AMD) and elevated serum cholesterol levels. Because the retina has high oxygen consumption, it is particularly susceptible to cellular damage caused by the production of free radicals and other by-products of oxygen metabolism. This means that, in theory, the antioxidant vitamins A, C and E and the carotenoids lutein and zeaxanthin could reduce the likelihood of AMD by a direct antioxidant mechanism. In addition, carotenoid supplementation could augment macular pigmentation and limit oxidative damage by increasing absorption of damaging wavelengths of light into the eye. Zinc might also be beneficial as it is an important cofactor for antioxidant enzymes.

Prominent lutein and antioxidant vitamin containing preparations include: *Icaps, Macushield, Occuvite Complete Capsules*, *Preservision Original*, *Preservision Lutein Capsules*, *Viteyes Original Formula Plus Lutein*, *Viteyes Original*, *Visionace Plus* and *Visionace Original.* These products are health-food supplements marketed to maintain "eye health"; they are not licensed for prophylaxis or treatment of any medical conditions, including prevention of progression of AMD. It has been estimated that the prescribing of these products in primary care costs approximately £1.6Mpa across the NHS.

Review of the evidence

The evidence base for the use of antioxidant vitamins and minerals derives from a single randomised controlled trial, known as the Age-Related Eye Disease Study (AREDS). This trial assessed the effect of high doses of zinc and/or antioxidant vitamins (vitamin C 500mg, vitamin E 400 units, beta-carotene 15mg) on the development and progression of age related macular degeneration and on visual acuity in 4,757 people. Overall the study concluded, from a pooled analysis of results, that daily oral supplementation with antioxidant vitamins and minerals reduced the likelihood of developing advanced AMD by 25%. However, patients were actually allocated to a number of different groups dependent upon the severity of their disease and analysis of these results reveals that:

- participants who initially had no AMD had less than 1% chance of losing vision from AMD during the 6.3 year mean follow-up period of the study.
- for those with early AMD at the outset, antioxidants plus zinc did not slow disease progression to intermediate AMD.
- the low event rate made it impossible to assess whether any of the treatment effects identified were of genuine significance or simply chance findings.
- the study was conducted using a well-nourished American population.

Even the authors of the study concluded that treatment benefit was modest and that participants in all treatment arms continued to progress to advanced AMD and lose vision over time.

A second study, AREDS2, was set up to establish whether adding carotenoids lutein and zeaxanthin or omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid) or both to the original AREDS formulation might further reduce the risk of progression to advanced AMD. This study concluded that the addition of any of these combinations to the original AREDS formulation did nothing to further reduce the risk of progression to advanced AMD.

A subsequent review undertake by the Cochrane collaboration published in 2012 concluded that there is insufficient evidence to support any speculative conclusion drawn from the

AREDS data at present. Only a large-scale RCT set up to replicate the AREDS results could provide reassurance that any of the AREDS conclusions are correct. Cochrane also expressed concern about the risks of long-term vitamin supplementation, particularly in smokers and those with vascular disease. A further systematic Cochrane review has also concluded that there is little evidence to support the use of antioxidant multivitamin combinations to prevent progression of AMD.

While there is insufficient evidence to recommend lutein and zeaxanthin supplements, eating a healthy diet rich in oily fish, dark green leafy vegetables and fresh fruit is likely to improve concentrations of macular pigment in the fundus and unlikely to do any harm. Particularly good foods for high lutein and zeaxanthin content include: egg yolk, maize (corn), orange pepper, kiwi fruit, grapes, spinach, kale, orange juice, courgette and different kinds of squash. For further information patients can be referred to the Macular Society leaflet 'Nutrition and your eyes'.

As identified by Cochrane, the use of long-term high doses of vitamins and minerals is not without risk. For example, beta-carotene has been found to increase the risk of lung cancer in smokers, vitamin E has been linked with an increased risk of heart failure in people with diabetes or vascular disease and zinc may increase the risk of bladder or kidney problems.

Many of these products listed now offer AREDS or AREDS2 based formulations (e.g. *ICaps*, *Viteyes*, *Preservision*).

The table below summarizes the current expenditure on prescribing of these products for each of the Lincolnshire CCGs:

	Annual Cost 2014/15
Lincolnshire East CCG	£12,216 (predominantly *MacuShield* and *Icaps*)
Lincolnshire West CCG	£6,739 (predominantly *MacuShield*, *Icaps* and *Preservision Lutein*)
South Lincolnshire CCG	£6,466 (predominantly *MacuShield* and *Icaps*)
South West Lincolnshire CCG	£3,080 (predominantly *MacuShield*)
Lincolnshire	£28,501

PACEF Recommendations:
All patients currently receiving any of the lutein or antioxidant vitamins on prescription should have their treatment reviewed at their next review appointment. All of these products are designated RED-RED and are not approved for use on the *Lincolnshire Joint Formulary*. All prescriptions should be stopped and patients advised to purchase their preferred supplement from pharmacies, health supplement retailers or reputable online retailers if they wish to continue with treatment. All new requests to prescribe these products should be refused. Patients concerned about vitamin and mineral supplementation should be advised to review their diet with a view to increasing consumption of foods containing high levels of lutein and zeaxanthin. The Macular Society leaflet 'Nutrition and your eyes' provides useful supporting information. The potential saving across Lincolnshire if all inappropriate prescribing of lutein and antioxidant vitamin preparations were stopped is £28,500pa.

References

1. 'Lutein and antioxidant vitamins for prevention of age-related macular degeneration (AMD)', *PresQIPP Bulletin* 86 (December 2014).
2. 'Nutritional supplements for macular degeneration', *Drug and Therapeutics Bulletin*, Vol 44 No 2 (February 2006).

3. Age-Related Eye Disease Study Research Group, 'A randomized, placebo controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene and zinc for age-related macular degeneration and vision loss', *Arch Ophthalmol* 2001; 119:1417-36.
4. The Age-Related Eye Disease Study 2 (AREDS2) Research Group, 'Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial. *JAMA* 2013; 309(19): 2005-2015.
5. Evans JR., Lawrenson JG., Antioxidant vitamin and mineral supplements for preventingf age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2012, Issue 6.
6. Evans JR., Lawrenson JG., Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database of Systematic Reviews* 2012, Issue 11.

QIPP OPPORTUNITY: *LOWER COST BRANDED PRODUCTS*

Up to date information on sourcing preferred lower cost branded products is provided.

As you will be aware, over the last few years the range of lower cost branded products equivalent to established originator brands has expanded significantly. In recent issues of the *PACE Bulletin*, PACEF have endorsed the preferential prescribing of:

- Galantamine 8mg and 16mg sustained release capsules (*Galantex XL*, *Gatalin XL*).
- Methylphenidate hydrochloride 18mg and 36mg sustained release tablets (*Xenidate XL*).
- Quetiapine 50mg, 150mg, 200mg, 300mg and 400mg modified release tablets (*Biquelle XL*, *Zaluron XL*).
- Ropinirole 2mg, 4mg and 8mg sustained release tablets (*Repinex XL*)
- Tolterodine 2mg and 4mg sustained release capsules (*Neditol XL*).

This is in addition to an already established range of lower cost brands promoted as QIPP opportunities by the Prescribing and Medicines Optimisation (PMOS) team.

One of the most common requests received by the PMOS team from prescribers, dispensers and community pharmacists is for further information on sourcing lower cost branded products. Included as an Appendix to this issue of the *Bulletin* is a table detailing, for each proposed switch: (1) the manufacturer of each product with contact details; (2) the wholesalers who supply each product and (3) confirmation of stock availability. We hope that this table answers most of the immediate questions in relation to supply of these products. It is strongly recommended that practices considering a switch to a preferred lower cost brand should inform their local community pharmacy or pharmacies of their intention to do so before issuing prescriptions.

RAPID DRUG ASSESSMENT*: INSULIN DEGLUDEC 100 UNITS/LIRAGLUTIDE 3.6MG PER ML INJECTION (XULTOPHY)*

In view of safety concerns over high-dose fixed combination insulin preparations and the high cost of insulin analogues in comparison to conventional insulins, insulin degludec 100 units/liraglutide 3.6mg/mL injection (*Xultophy*) is not approved for use.

Insulin degludec 100 units/liraglutide 3.6mg/mL injection (*Xultophy*) is the first fixed dose combination of an insulin plus a glucagon-like peptide-1 (GLP-1) analogue to gain a UK marketing authorisation. It is licensed for the treatment of adults with type 2 diabetes to improve glycaemic control in combination with oral glucose lowering medicines when these alone or combined with basal insulin do not provide adequate glycaemic control.

All three currently available GLP-1 analogues, exenatide, liraglutide and lixisenatide, are approved for use on the *Lincolnshire Joint Formulary*; they are all licensed for use as adjunctive therapy to basal insulin with or without other glucose lowering medicines. The only exception is once weekly exenatide (*Bydureon*) which is not licensed to be used in combination with insulin.

Supporting evidence for *Xultophy* comes from a series of 26 week and 52 week trials comparing the efficacy of the *Xultophy* combination with either insulin degludec or liraglutide prescribed alone in patients receiving concomitant therapy with other antidiabetic medication. Results from these trials demonstrate a statistically significant reduction in HbA1c levels beyond that achieved with either insulin degludec or liraglutide therapy and confirm that combination insulin degludec/liraglutide therapy is potentially more effective than each of the components prescribed separately. Secondary outcome data from the trials also demonstrated a reduction in the dose of insulin required compared to insulin degludec prescribed alone. Also, patients in the *Xultophy* groups showed either a slight reduction in weight or a small weight gain compared to more significant weight gain in the insulin groups.

In terms of adverse effects, *Xultophy* demonstrates a lower risk of hypoglycaemia than insulin alone, but a higher risk than would be expected with liraglutide therapy. By contrast the incidence of GI side effects is lower with the combination product compared to liraglutide alone, probably due to the smaller incremental dose increases possible within the restriction of the fixed dose combination.

There is no comparative data between *Xultophy* and any other insulin/GLP-1 combination product. There is also a lack of long term safety and efficacy data.

Xultophy contains 1 unit of insulin degludec and 0.036mg liraglutide in each dose step (100units/3.6mg/mL). The MHRA *Drug Safety Update* for April 2015 has already identified *Xultophy* as a high strength fixed combination insulin product presenting a particularly high risk of error (see later). Any fixed dose combination also has the disadvantage of limited flexibility of dosage (for example, the dose of one component cannot be altered without altering the dose of the other).

At the maximum dose of 50 units daily, *Xultophy* is £30 cheaper per month than the individual cost of insulin degludec and liraglutide prescribed separately. A significantly lower cost option would be to prescribe an alternative long-acting conventional insulin in combination with liraglutide prescribed separately.

PACEF Recommendation:

PACEF acknowledge that it is now established practice to use insulin in combination with a GLP-1 analogue and that dose steps enable a much more sensitive dosing of liraglutide. Nonetheless, where combination therapy is considered necessary, conventional insulins rather than insulin analogues are preferred. In the absence of comparative data between *Xultophy* and other GLP1/insulin combinations it is difficult to justify the increased cost. In addition, long-term safety and efficacy data is lacking and significant safety issues remain around the use of high-dose, fixed combination insulin products. As a result of this, insulin degludec 100 units/liraglutide 3.6mg/mL injection (*Xultophy*) is designated RED-RED and is not approved for inclusion in the *Lincolnshire Joint Formulary* at this time.

RAPID DRUG ASSESSMENT: *GLYCOPYRRONIUM BROMIDE 2% ROLL-ON APPLICATOR (UNLICENSED SPECIAL)*

PACEF have approved a single patient request for glycopyrronium bromide 2% roll-on applicator for the treatment of palmar hyperhidrosis that has failed to respond to oral therapy and iontophoresis. There is evidence of effectiveness from case reports and small studies. The cost of a 50ml roll-on applicator is £66.56.

PACEF Recommendation:
Subject to specialist initiation and initial supply from ULH, glycopyrronium bromide 2% roll-on applicator is designated AMBER without shared care. If supply problems exist in primary care, the product will need to continue to be sourced through secondary care.

PRODUCT DISCONTINUATION: *MORPHINE SULFATE SUSTAINED RELEASE TABLETS (FILNARINE SR)*

Teva UK have discontinued their brand of morphine sulfate sustained release tablets (*Filnarine SR*). Both *Morphgesic* SR tablets (Amdipharm Mercury) and *Zomorph* sustained release capsules (Archimedes) remain available at a significantly lower price than *MST Continus* SR tablets (Napp) (see updated cost comparison below)

	MST	Morphgesic	Zomorph
5mg	£3.29	-	-
10mg	£5.20	£3.85	£3.47
15mg	£9.10	-	-
30mg	£12.47	£9.24	£8.30
60mg	£24.32	£18.04	£16.20
100mg	£38.50	£28.54	£21.80
200mg	£81.34	-	£43.60

Prices compiled from *MIMS*, July 2015

It has been estimated that specifying a lower cost brand of morphine sulfate MR tablets/capsules rather than prescribing generically or as *MST Continus* could generate cost savings across Lincolnshire of approximately £59,456p.a.

Key product characteristics of the two preferred products are tabulated below:

*Morphgesic t*ablets

	Pros	Cons
Available strengths	Available in four strengths (10mg, 30mg, 60mg, 100mg)	Lower strengths (5mg and 15mg) and 200mg are not available.
Appearance	Tablet colour and packaging resemble *MST Continus.*	
Generic prescribing		Generic prescribing will result in the *MST Continus* reimbursement price being paid.
Bioequivalence	*Morphgesic* tablets have been shown to be bioequivalent with *MST Continus.*	
Interface issues		*Morphgesic* tablets are not used within ULH
Cost	Significantly lower cost than *MST Continus*.	Higher cost than *Zomorph.*

Zomorph capsules

	Pros	**Cons**
Available strengths	Available in five strengths (10mg, 30mg, 60mg, 100mg and 200mg)	Lower strengths (5mg and 15mg) are not available.
Appearance		Does not resemble *MST Continus*
Generic prescribing		Risk of confusion with *MXL* once daily capsule if prescribed generically
Bioequivalence	*Zomorph* capsules have been shown to be bioequivalent with *MST Continus*	
Interface issues	*Zomorph* capsules is the MR morphine formulation of choice within ULH	
Swallowing difficulties	*Zomorph* capsules can be opened and the contents sprinkled onto a spoonful of semi-solid food (e.g. yoghurt) or used to make a suspension that can be administered via a gastric or gastronomy feeding tube.	
Cost	Significantly lower cost than *MST Continus* and *Morphgesic*.	

PACEF Recommendation

Prescribers are urged to ensure that all new prescribing of morphine modified release specifies either *Morphgesic* or *Zomorph* by brand depending on prescriber preference or the needs of the patient. Where possible, existing MR morphine prescribing should be standardized around branded *Morphgesic* or *Zomorph*; it is acknowledged that some residual *MST Continus* prescribing will need to remain, particularly where strengths only available in the *MST Continus* range are in use (5mg and 15mg). *Filnarine SR* has recently been discontinued.

PRODUCT SUPPLY PROBLEM: *CREON 40,000 (PANCREATIN) 40,000 GASTRO-RESISTANT CAPSULES*

Advice on how to manage patients during the current supply problem with *Creon 40,000* (pancreatin) capsules.

We have been notified by BGP Products Ltd that *Creon 40,000* capsules (pancreatin) are currently unavailable. Supply of *Creon 25,000* and *Creon 10,000* remains unaffected and prescribers are advised to transfer patients over to the lower strength formulations. In order to minimize the tablet burden, prescribers are advised to transfer to *Creon 25,000*, where possible. The following table gives useful information on equivalent doses:

Current *Creon 40,000* dose	**Equivalent dose using *Creon 25,000***	**Equivalent dose using *Creon 10,000***
1 capsule = 40,000 lipase units	2 capsules = 50,000 lipase units	4 capsules = 40,000 lipase units
2 capsules = 80,000 lipase units	3 capsules = 75,000 lipase units	8 capsules = 80,000 lipase units

NICE TECHNOLOGY APPRAISAL 336: *EMPAGLIFLOZIN IN COMBINATION THERAPY FOR TREATING TYPE 2 DIABETES* (MARCH 2015)

- Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating type 2 diabetes, only if: a sulfonylurea is contraindicated or not tolerated, or the person is at significant risk of hypoglycaemia or its consequences.
- Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination with: metformin and a sulfonylurea or metformin and a thiazolidinedione.
- Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

The following table summarizes the key characteristics of each of the three sodium-glucose co-transporter 2 (SGLT2) inhibitors currently approved for use through the *Lincolnshire Joint Formulary*:

	Canagliflozin (*Invokana*)	**Dapagliflozin (*Forxiga*)**	**Empagliflozin (*Jardiance*)**
Licensed indications	In adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin,	In adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin,	In adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin,
NICE TA	√	√	√
Monotherapy	X	X	X
Dual therapy with metformin	√	√	√
Triple therapy Metformin + sulfonylurea	√	X unless part of clinical trial	√
Triple therapy Metformin + pioglitazone	√	X	√
With insulin With or without other antidiabetic drugs	√	√	√
Use in renal impairment	Should not be initiated in patients whose eGFR<60ml/min/1.73 m2. In patients tolerating canagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m2, the dose of should be adjusted to or maintained at 100 mg once daily. canagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m2.	Not recommended eGFR<60ml/min/1.73 m2	Should not be initiated in patients whose eGFR<60ml/min/1.73 m2. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m2, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m2.
Available with metformin	√ Canagliflozin/metformin 50mg/850mg & 50mg/1g (*Vokanamet*)	√ Dapagliflozin /metformin 5mg/850mg & 5mg/1g (*Xigduo*)	X

Dose range	100mg od increasing to 300mg daily if required	10mg once daily, lower 5mg dose may be needed if used with insulin or sulfonylureas	10mg once daily increasing to 25mg if necessary.
Cost per month	£39.20 – 100mg £49.99 – 300mg	£36.59 5 and 10mg	£36.59 10 and 25mg

PACEF Recommendations:

Empagliflozin tablets 10mg and 25mg (*Jardiance*) are designated GREEN within NICE approved indications and are available for use through the *Lincolnshire Joint Formulary.* On grounds of cost, empagliflozin and dapagliflozin as recommended as the first-line SGLT2 inhibitors of choice (see table). In line with NICE guidance, SGLT2 inhibitors should only be considered as part of dual therapy with metformin as detailed in the NICE Pathway for blood glucose lowering therapy for type 2 diabetes (June 2013) (i.e. if HbA1c remains > 6.5% despite monotherapy). A SGLT-2 inhibitor should only be considered at this stage where a sulfonylurea is contraindicated or not tolerated or if the person is at significant risk of hypoglycaemia or its consequences. Prescribers should also be mindful of the significant increased cost of SGLT-2 inhibitors compared to potential alternatives such as DPP- 4 inhibitors. There is also a significant increased risk in patients with moderate to severe renal impairment or advanced age (75 and older). Canagliflozin and empagliflozin are approved by NICE for triple therapy in combination with metformin and a sulfonylurea or metformin and pioglitazone. Combination use of a SGLT2 inhibitor and insulin is also approved further down the pathway. Canagliflozin, dapagliflozin and empagliflozin are not recommended by NICE for monotherapy and are designated RED-RED for this indication. Due to their mode of action, none of the SGLT2 inhibitors should be initiated in patients with renal impairment with an eGFR of <60 ml/min/1.73 m2. However, those patients who have previously shown they can tolerate and respond to canagliflozin or empagliflozin treatment can continue until eGFR is persistently below 45 mL/min/1.73 m2.

NICE TECHNOLOGY APPRAISAL 337: *RIFAXIMIN FOR PREVENTING EPISODES OF OVERT HEPATIC ENCEPHALOPATHY* (MARCH 2015)

Rifaximin (*Targaxan*) is recommended by NICE for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.

Notes

Rifaximin (*Targaxan*) is a semi-synthetic derivative of the antibiotic rifamycin licensed for the reduction in recurrence of overt hepatic encephalopathy. Rifaximin decreases intestinal production and absorption of ammonia which is thought to be responsible for the neurocognitive symptoms of hepatic encephalopathy and has been shown to be effective in delaying the recurrence of acute episodes. It has been studied in clinical trials as monotherapy or in combination with lactulose for the treatment of adults with liver disease who have had prior acute episodes of hepatic encephalopathy (grade II-IV). A recent study showed that over a 6-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than placebo. Rifaximin treatment also significantly reduced the risk of hospitalization due to hepatic encephalopathy. The incidence of adverse events was similar in the rifaximin group and the placebo group. The cost of the treatment is £259.23 per month. In the pivotal study, 91% of the patients were using concomitant lactulose. The recommended dose of rifamixin is 550 mg twice a day. The clinical benefit was established from a controlled study in which subjects were treated for 6 months. Treatment beyond 6 months should take into consideration the individual balance between benefits and risks, including those associated with the progression of hepatic dysfunction.

There is a second licensed rifaximin product (*Xifaxanta* – 200mg tablets) which is licensed for the treatment of non-invasive travellers' diarrhoea. Rifamixin tablets 200mg (*Xifaxanta*) are not approved for local use and are designated RED/RED.

PACEF Recommendation:
Rifaximin tablets 550mg *(Targaxan)* for the reduction in recurrence of overt hepatic encephalopathy have been approved for use by NICE. The product is already available for this indication through the *Lincolnshire Joint Formulary*. Designation: AMBER

MEDICINES AND HEALTHCARE REGULATORY AGENCY: *DRUG SAFETY UPDATE* (APRIL 2015)

HYDROXYZINE (*ATARAX*, *UCERAX*): RISK OF QT INTERVAL PROLONGATION AND TORSADE DE POINTES

Hydroxyzine is an antihistamine used to treat pruritus in adults and children and anxiety in adults. The maximum adult daily dose of hydroxyzine is now 100 mg.

A European review of the safety and efficacy of hydroxyzine has been undertaken following concerns over associated heart rhythm abnormalities. The review concluded that hydroxyzine is associated with a small risk of QT interval prolongation and Torsade de Pointes. Such events are most likely to occur in patients who already have risk factors for QT prolongation, such as: (1) concomitant use of medicines that prolong the QT interval; (2) cardiovascular disease; (3) family history of sudden cardiac death; (4) significant electrolyte imbalance (low potassium or magnesium levels) and (5) significant bradycardia.

Advice for healthcare professionals:

- Do not prescribe hydroxyzine to people with a prolonged QT interval or for those who have risk factors for QT interval prolongation.
- Do not use hydroxyzine in the elderly as they are more susceptible than younger patients to the side effects.
- Consider the risks of QT interval prolongation and Torsade de Pointes before prescribing to patients taking medicines that lower heart rate or potassium levels.
- The maximum daily dose of hydroxyzine is now:
    - 100 mg for adults.
    - 50 mg for the elderly (if use cannot be avoided).
    - 2 mg per kg body weight for children up to 40 kg in weight.
- Prescribe the lowest effective dose for as short a time as possible.
- Continue to report any suspected side effects to hydroxyzine or any other medicine on a Yellow Card.

CODEINE FOR COUGH AND COLD: RESTRICTED USE IN CHILDREN

Codeine is an opioid medicine that is authorised for pain relief and to treat the symptoms of cough and cold. Codeine is converted into morphine by an enzyme called CYP2D6. Some people (known as ultra-rapid metabolisers) convert codeine into morphine faster than others. This results in high morphine levels in the blood, which can cause toxic effects such as breathing difficulties.

In 2010 the UK Commission on Human Medicines advised that over-the-counter liquid medicines that contain codeine should not be used for cough suppression in people under 18. A European review has been conducted into the benefits and risks of using codeine to

treat cough and cold symptoms in children. This followed the 2013 review of codeine for pain relief in children, which was in response to some fatal and life-threatening cases of morphine intoxication. The review concluded that there is limited evidence that codeine is effective for treating cough and cold symptoms in children. Although impact of age on codeine metabolism is not fully understood, the current evidence suggests that children under 12 are at a higher risk of serious side effects than children over 12. In addition, codeine can worsen symptoms in adolescents who already have problems with breathing.

In line with recommendations for codeine when used for pain relief, codeine must not be taken by patients of any age known to be ultra-rapid metabolisers or by breastfeeding mothers. Codeine can be passed through breast milk, which can harm the baby.

PACEF Recommendation:
When prescribing or dispensing codeine-containing medicines for coughs and colds, remember that codeine is contraindicated in: (1) children younger than 12 years old; (2) patients of any age known to be CYP2D6 ultra-rapid metabolisers and (3) breastfeeding mothers. Codeine is also not recommended for adolescents (12 to 18) who have problems with breathing.

HIGH STRENGTH, FIXED COMBINATION AND BIOSIMILAR INSULIN PRODUCTS: MINIMISING THE RISK OF MEDICATION ERROR

Several new insulin products have come to market recently including three high strength insulins which have concentrations greater than 100 units/mL (*Tresiba*, *Humalog* and *Toujeo*), a fixed combination of insulin degludec and liraglutide (*Xultophy*) (see earlier) and a biosimilar of insulin glargine (*Abasaglar*).

Details of the new products are as follows:

Key feature	Active substance	Brand name	Strengths available Units/ml	Administration device
High strength	Insulin degludec	*Tresiba*▼	100 200	*FlexTouch* Prefilled pen
	Insulin lispro	*Humalog*	100 200	*KwikPen* Prefilled pen
	Insulin glargine	*Lantus*	100	*SoloSTAR* Prefilled pen
		Toujeo▼	300	
Fixed combinations	Insulin degludec and liraglutide	*Xultophy*▼	100units/ml of insulin degludec and 3.6mg/ml of liraglutide	Prefilled pen
Biosimilar	Insulin glargine	*Abasaglar*▼	100 units/ml cartridge	Lilly reusable pen
			100	*KwikPen* Prefilled pen

Healthcare professionals and patients will need to ensure that they fully understand the insulin strength of these products and how to use them correctly to minimise the risk of medication errors (such as the wrong insulin dose being administered).

High strength insulin products

High strength insulin products have been developed for patients with large daily insulin requirements to reduce the number and volume of injections.

The dose step

The 'dose step' is a new term to define how patients dial up the required drug dose on the prefilled pen.

For *Lantus*, *Toujeo* and both strengths of *Humalog*:

- one dose step on the prefilled pen is equivalent to one unit of insulin.

In contrast, with *Tresiba*:

- one dose step on the 100 units/mL pen is equivalent to one unit of *Tresiba.*
- one dose step on the 200 units/mL pen is equivalent to 2 units of *Tresiba.*

Dose conversion when switching between standard and high strength insulin products

For all the insulin products in the table above, the required dose is displayed in the dose counter window of the prefilled pen.

For *Humalog* 100 and 200 units/mL *KwikPens*, and for *Tresiba* 100 and 200 units/mL *FlexTouch* pens:

- there is **no need for dose conversion** when transferring patients from the standard to high strength version or vice versa.

However, *Toujeo* is **not bioequivalent** to *Lantus*:

- dose adjustment is needed when patients are switched from *Lantus* or other basal insulins to *Toujeo* or vice versa.

***Xultophy*: insulin in fixed combination with liraglutide**

Xultophy is the first product to combine insulin with another injectable treatment; it combines insulin degludec 100 units/mL with liraglutide 3.6 mg/mL in a prefilled pen. Liraglutide (*Victoza*) is a glucagon-like peptide-1 (GLP-1) receptor agonist licensed for the treatment of type 2 diabetes. One dose step on the *Xultophy* prefilled pen is equivalent to one unit of insulin degludec and 0.036 mg of liraglutide. For further information, see the *Xultophy* summary of product characteristics and the PACEF evaluation of the product earlier in the *Bulletin.*

***Abasaglar*: biosimilar insulin**

Abasaglar is a biosimilar insulin based on insulin glargine 100 units/mL (*Lantus*); it is licensed for the treatment of diabetes in adults, adolescents, and children aged 2 years and above. *Abasaglar* has been shown to be equivalent to *Lantus* in its pharmacokinetic and pharmacodynamic properties. However, as with other biosimilar medicines, dose adjustment may be needed for some patients. For further information, see the *Abasaglar s*ummary of product characteristics.

Advice for healthcare professionals:

Before starting treatment with a high strength, fixed combination or biosimilar insulin product:

- consult the summary of product characteristics and any educational material.
- ensure that patients read and understand the patient leaflet and any patient education material.
- ensure that patients receive appropriate training on the correct use of the product
- give patients a patient booklet and Insulin Passport (or safety card).
- warn patients only to use insulin as they have been trained because using it any other way may result in a dangerous overdose or underdose.

Monitor glucose levels closely after starting a new treatment and in the following weeks. It may be necessary to adjust doses and timing of concurrent rapid acting or short acting insulin products and other antidiabetic treatments.

PACEF Comment

As yet, not all of the products included within this MHRA update are available in the UK. Of those that have been launched, *Humalog* 200 units/ml has not yet been evaluated by PACEF and remains RED-RED until an evaluation is completed and published. Insulin degludec 100 units/liraglutide 3.6mg/mL injection (*Xultophy*) is evaluated in this edition of the *Bulletin* and designated RED-RED due to safety concerns over high-dose fixed combination insulin preparations and the high cost of insulin analogues in comparison to conventional insulins.

Currently insulin degludec is designated AMBER without shared care and is included in the *Lincolnshire Joint Formulary*. It is restricted for use in the following patient groups:

- **patients with type 1 DM who have recurrent admissions with diabetic ketoacidosis due to poor adherence.**
- **patients with type 1 DM with problematic or recurrent nocturnal hypoglycaemia on other long-acting analogues and are not suitable for insulin pump therapy.**
- **for a small number of patients with type 2 DM with significant insulin resistance who might otherwise need large doses of Humulin R U500 insulin.**

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Arden and Greater East Midlands Commissioning Support Unit

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Generic/Higher Cost Branded Product	Recommended Lower Cost Equivalent Branded Product	Manufacturer	Manufacturer Phone Number	Wholesalers Where Stock is Available	In stock as at 17th June 2015 Y/N
Co-codamol 30/500	Switch to branded *Zapain*	Amdipharm Mercury (AMCo) Group	0208 6498500	Alliance	Y
Fentanyl Patches	Switch to branded *Fencino*	DB Ashbourne Ltd	01858 525643	AAH, Alliance, Maltbys (Co-op), Mawdsleys & Phoenix	Y
	Switch to branded *Matrifen*	Teva UK Ltd	0800 590502	AAH, Alliance, Maltbys (Co-op) Mawdsleys & Phoenix	Y
	Switch to branded *Mezolar*	Sandoz Ltd	01276 698020	AAH, Alliance, Maltby's (Co-op) Mawdsleys, Phoenix	Y
	Switch to branded *Opiodur*	Pfizer Ltd	01304 616161	Alliance	Y
Galantamine SR capsules / *Reminyl XL*	Switch to branded *Galantex XL* 8mg and 16mg only (24mg not made in this brand)	Creo Pharma Ltd	01371 822022	Alliance Specials, Maltby's (Co-op) Quantum Pharmaceuticals	Y
	Switch to branded *Gatalin XL*	Aspire Pharma Ltd	01730 231148	AAH, Alliance, Maltby's (Co-op) Mawdsleys & Phoenix	Y
Isosorbide mononitrate MR tablets 60mg	Switch to branded *Monomil XL 60*	Teva UK Ltd	0800 590502	AAH, Alliance, Maltby's (Co-op) Mawdsleys & Phoenix	Y
Methylphenidate SR/ *Concerta XL*/ *Matoride XL* 18mg/36mg	Switch to branded *Xenidate XL*	Mylan	01707 853000	AAH, Alliance, Maltby's (Co-op) Mawdsleys & Phoenix	Y

Morphine Sulphate MR tabs / *MST Continus*	Switch to branded *Morphgesic SR*	Amdipharm Mercury (AMCo) Group	0208 6498500	Alliance	Y
	Switch to branded *Zomorph SR*	Archimedes Pharma UK Ltd	0118 9315060	AAH	Y
Oxycodone MR	Switch to branded *Longtec MR*	Qdem Pharmaceuticals	01223 426929	AAH, Alliance & Phoenix	Y
	Switch to branded *Reltebon*	Actavis UK Ltd	01271 311200	AAH, Alliance, Maltbys (Co-op), Mawdsleys, Norchem & Phoenix	Y
Oxycodone Standard Release	Switch to branded *Lynlor*	Actavis UK Ltd	01271 311200	AAH, Alliance, Maltbys (Co-op), Mawdsleys, Norchem & Phoenix	Y
	Switch to branded *Shortec*	Qdem Pharmaceuticals	01223 426929	AAH, Alliance & Phoenix	Y
Quetiapine SR tablets / *Seroquel XL*	Switch to branded *Biquelle XL*	Aspire Pharma Ltd	01730 231148	AAH, Alliance, Maltby's (Co-op) Mawdsleys & Phoenix	Y
Quetiapine SR tablets / *Seroquel XL*	Switch to branded *Ebesque XL*	DB Ashbourne Ltd	01858 525643	AAH, Alliance, Maltbys (Co-op), Mawdsleys & Phoenix	Y
Quetiapine SR tablets / *Seroquel XL*	Switch to branded *Mintreleq XL*	CEB Pharma Ltd	01353 887100	Alliance Maltby's (Co-op)	Y
Quetiapine SR tablets / *Seroquel XL*	Switch to branded *Zaluron XL*	Fontus Health Ltd	0121 6614615	Alliance, Phoenix	Y
Ropinirole SR / *ReQuip XL* 2mg/4mg/8mg tabs	Switch to branded *Repinex XL*	Aspire Pharma Ltd	01730 231148	AAH, Alliance, Maltby's (Co-op) Mawdsleys & Phoenix	Y
Tolterodine MR capsules (Detrusitol XL)	Switch to branded *Neditol XL*	Aspire Pharma Ltd	01730 231148	AAH, Alliance, Maltby's (Co-op)	Y

				Mawdsleys & Phoenix	
Venlafaxine MR caps / Efexor XL	Switch to branded branded *Venaxx XL*	Amdipharm Mercury (AMCo) Group	0208 6498500	Alliance	Y
	Switch to branded *Depefex XL*	Chiesi Ltd	0161 4885555	AAH, Alliance & Phoenix	Y