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 15 **October 2015**

What's new this month?

- **Following an assessment of the IMPROVE-IT trial, it is now acknowledged that statin-ezetimibe combination therapy may have a role in patients requiring high-intensity statin therapy post- Acute Coronary Syndrome (ACS) (i.e. atorvastatin 80mg) who are either unable to tolerate such a high dose of atorvastatin or who are unable to achieve sufficient non HDL-C reduction on atorvastatin 80mg alone. Outside of this context, ezetimibe retains an extremely limited role (see page 5).**
- **Lincolnshire Partnership Foundation Trust have issued new guidance on the use of sodium valproate, carbamazepine and lamotrigine in women with mental health problems of childbearing age (see page 7).**
- **In collaboration with ULH microbiologists, PACEF have reviewed the *Formulary* status of some key antibiotics used for the treatment of resistant infections. In particular, fidaxomicin 200mg tablets (*Dificlir*) are now designated AMBER without shared care for the treatment of *Clostridium difficile* infection subject to the advice of a microbiologist (see page 8).**
- **Following a reduction in price of the 300mg strength of canagliflozin (*Invokana*) tablets, all three SGLT2 inhibitors are now approved as alternative options where an SGLT2 inhibitor is indicated through the *Lincolnshire Joint Formulary* (see page 9).**
- **Recent supply problems with naftidrofuryl 100mg capsules are now resolved restoring naftidrofuryl as the preferred treatment for intermittent claudication in people with peripheral arterial disease (PAD). Cilostazol (*Pletal*) is no longer PACEF approved for this condition (see page 10).**
- **The MHRA have reiterated and strengthened guidance designed to mimimize the risk of patients on denosumab or bisphosphonates developing osteonecrosis of the jaw (see page 11).**
- **The MHRA have highlighted increasing reports of eye irritation with latanoprost 50 microgram per ml eye drops (*Xalatan*) since reformulation. Prescribers are reminded that latanoprost 50 microgram per ml eye drops should always be prescribed generically and that the alternative second line treatment is travoprost 40microgram per ml (*Travatan*) or third line bimatoprost 100mcg per ml (*Lumigan*) (see page 12).**
- **In a recent incident in Lincolnshire, a patient allergic to peanut/arachis oil was unwittingly prescribed peppermint oil capsules (*Colpermin*), a peanut oil containing preparation. Fortunately, the patient came to no harm. Prescribers are alerted to the risk of peanut allergy sufferers being exposed to peanut oil as a constituent of peppermint oil capsules (*Colpermin*) (see page 12).**

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SUMMARY OF PACEF DECISIONS: *AUGUST 2015 UPDATE*

Drug	**Indication(s)**	**Traffic Light and *Joint Formulary* Status**
Canagliflozin 100mg and 300mg tablets (*Invokana*) (Janssen Cilag)	In adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin.	Recommended as a treatment option when an SGLT2 inhibitor is indicated in combination with metformin; designation GREEN. Also approved by NICE for triple therapy in combination with metformin and a sulfonylurea or metformin and pioglitazone; designation GREEN. Not recommended by NICE for monotherapy; RED-RED for this indication. Included in the *Lincolnshire Joint Formulary* for use within NICE criteria.
Cangrelor 50mg powder for solution for injection or infusion (Kengrexal) (MDCO)	For co-administration with aspirin for the prevention of thrombotic events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) when an oral P2Y12 inhibitor has not been given and is not feasible or desirable.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Cefixime 200mg tablets (*Suprax*) (Sanofi)	For respiratory tract infections and urinary tract infections	RED for prescribing by Sexual Health only. Included in the *Lincolnshire Joint Formulary*.
Chloramphenicol 250mg capsules	Reserved for the treatment of life-threatening infections, particularly those caused by *Haemophilus influenza* and also typhoid fever	RED Included in the *Lincolnshire Joint Formulary*.
Cilostazol tablets 50mg and 100mg (*Pletal*)	Improvement of maximal and pain free walking distances in patients with intermittent claudication who do not have rest pain or evidence of peripheral tissue necrosis	RED-RED Removed from the *Lincolnshire Joint Formulary* for this indication.
Dapagliflozin (*Forxiga*) 5mg and 10mg tablets	In adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin.	Recommended as a treatment option when an SGLT2 inhibitor is indicated in combination with metformin; designation GREEN.

		Not recommended by NICE for monotherapy; RED-RED for this indication. Included in the *Lincolnshire Joint Formulary* for use within NICE criteria.
Empagliflozin (*Jardiance*) 10mg and 20mg tablets	In adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin.	Recommended as a treatment option when an SGLT2 inhibitor is indicated in combination with metformin; designation GREEN. Also approved by NICE for triple therapy in combination with metformin and a sulfonylurea or metformin and pioglitazone; designation GREEN. Not recommended by NICE for monotherapy; RED-RED for this indication. Included in the Lincolnshire Joint Formulary for use within NICE criteria.
Everolimus 250microgram, 500microgram and 750microgram tablets (*Certican*) (Novartis)	For use in combination with tacrolimus and corticosteroids for prophylaxis of organ rejection in liver transplant patients.	RED-RED Not approved for use through the *Lincolnshire Joint Formulary* for this indication.
Fidaxomicin tablets 200mg (*Dificlir*) (Astellas)	For C.difficile infection	AMBER without shared care subject to recommendation by a microbiologist. *Joint Formulary* status changed from RED to AMBER.
Fosfomycin 3g sachets (unlicensed)	For use on the advice of a microbiologist for the treatment of uncomplicated lower urinary tract infections caused by multiple antibacterial resistant organisms when other antibacterials cannot be used	AMBER (without shared care); can be prescribed by a GP subject to microbiologist advice and availability in primary care. *Joint Formulary* status changed from RED to AMBER.
Latanoprost 50 microgram per ml eye drops (generic)	For the treatment of open angle glaucoma and ocular hypertension.	AMBER subject to initiation by an ophthalmologist. First line for the treatment of glaucoma and ocular hypertension, particularly in those with early mild disease. Included in the *Lincolnshire Joint Formulary*.
Latanoprost 50 microgram per ml eye drops (*Xalatan*) (Pfizer)	For the treatment of open angle glaucoma and ocular hypertension.	RED-RED. Should be prescribed generically.
Linezolid 600mg tablets (Zyvox) (Pfizer)	For nosocomial pneumonia, community acquired pneumonia and complicated SSTI in a hospital environment.	RED Included in the *Lincolnshire Joint Formulary*.
Naftidrofuryl 100mg capsules (generic/ *Praxilene*)	Peripheral vascular disorders	GREEN Generic prescribing preferred. Included in the *Lincolnshire Joint Formulary* for this indication.
Nintedanib 100mg and 150mg capsules (*Vargatef*)	For use in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy.	RED Approved for Inclusion in the *Lincolnshire Joint Formulary* for this indication.
Nintedanib 100mg and150mg capsules (*Ofev*)	For use in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF).	RED-RED subject to future assessment. Not currently included for use through the *Lincolnshire Joint Formulary*
Omalizumab 150mg per ml solution for injection in pre-filled syringe (*Xolair*) (Novartis)	For use as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent (12 years and above) patients with	RED Approved for Inclusion in the *Lincolnshire Joint Formulary* for this indication. Should only be initiated

	inadequate response to H1 antihistamine treatment and leukotriene antagonists. For use in patients (adults, adolescents and children (6 to <12 years of age) with convincing IgE (immunoglobulin E) mediated asthma.	within specialist centres. RED Included in the *Lincolnshire Joint Formulary* for this indication.
Pomalidomide 1mg, 2mg 3mg and 4mg capsules (*Imnovid*) (Celgene)	For use in combination with dexamethasone in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.	RED-RED Not approved for use through the *Lincolnshire Joint Formulary* for this indication.
Ustekinumab injection (Stelara) (Janssen-Cilag)	For use alone or in combination with methotrexate for the treatment of active psoriatic arthritis in adult patients when the response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.	RED Approved for Inclusion in the *Lincolnshire Joint Formulary* for this indication. For use only under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriatic arthritis.
Vancomycin capsules 125mg and 250mg	For pseudomembranous colitis and staphylococcal enterocolitis	AMBER without shared care subject to recommendation by a microbiologist. *Joint Formulary* status changed from RED to AMBER.
Vedolizumab 300mg injection (*Entyvio*) (Takeda)	For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist. For the treatment of adult patients with moderate to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist.	RED Approved for Inclusion in the *Lincolnshire Joint Formulary* for this indication. The license stipulates that treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis. RED-RED for this indication pending publication of NICE guidance.
Voriconazole 50mg and 200mg tablets (Vfend) (Pfizer)	For the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, fluconazole resistant serious invasive Candida infections (including *C. krusei*), serious fungal infections caused by *Scedosporium spp* and *Fusarium spp* in patients with progressive possibly life-threatening infections. Prophylaxis of invasive fungal infections in high risk allogeneic haematopoietic stem cell transplant recipients.	RED Included in the *Lincolnshire Joint Formulary* for these indications.

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

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.**

NEW TRIAL ASSESSMENT: *IMPROVE-IT*

Following an assessment of the IMPROVE-IT trial, it is now acknowledged that statin-ezetimibe combination therapy may have a role in patients requiring high-intensity statin therapy post- Acute Coronary Syndrome (ACS) (i.e. atorvastatin 80mg) who are either unable to tolerate such a high dose of atorvastatin or who are unable to achieve sufficient non HDL-C reduction on atorvastatin 80mg alone. Outside of this context, ezetimibe retains an extremely limited role

The Improved Reductions of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluated the effect of ezetimibe 10mg combined with simvastatin 40mg against simvastatin 40mg alone in 18,144 stable patients who had had acute coronary syndrome (ACS) and whose LDL-C levels were within guideline recommendations. Men and women (50 years and over) were eligible for inclusion if they had been hospitalized within the previous 10 days for ACS (i.e. acute MI, with or without ST-segment evaluation on ECG or high-risk unstable angina).

18,144 patients were recruited between October 2005 and July 2010 and randomized at 1147 sites in 39 countries. The average age of the patients was 64 years, 24% were women, 27% had diabetes, 88% had undergone coronary angiography, 70% had undergone percutaneous coronary intervention, 34% were already taking statins on entering the study.

PACEF Comment:
This trial was undertaken in a secondary prevention patient group with very specific entry criteria (i.e. hospitalized within the previous 10 days for ACS). The authors recognize that they evaluated patients who had an ACS and that the results are most relevant to that population. There is still no study that provides outcomes data for ezetimibe or simvastatin-ezetimibe in a primary prevention population.

Assuming standard medical and interventional treatment for ACS, patients were randomly assigned to simvastatin 40mg once daily plus ezetimibe 10mg or simvastatin 40mg plus placebo.

PACEF Comment:
A significant number of patients in Lincolnshire are currently taking atorvastatin, not simvastatin. This study does not provide outcomes data to answer the question as to whether addition of ezetimibe to atorvastatin improves CV outcomes compared to atorvastatin alone. The study authors recognize that things have moved on since

simvastatin 40mg and 80mg could be utilized as background statin therapy as they were during the data collection phase of this trial.

The study continued until each patient had been followed up for a minimum of 2.5 years. The primary efficacy end point was a composite of death from CVD, a major coronary event (e.g. non-fatal MI, unstable angina requiring hospital admission or coronary revascularisation) or non-fatal stroke. The secondary efficacy end points were: (1) a composite of death from any cause, major coronary event or non-fatal stroke; (2) a composite of death from CHD, non-fatal MI or urgent coronary revascularisation and (3) a composite of death from CV causes, non-fatal MI, hospitalization from unstable angina, all revascularisation and non-fatal stroke. After a median of 6 years, 42% of the patients in each group had discontinued the study medication without having died or without having had a primary end-point event.

PACEF Comment:
According to the study authors, this rate of attrition in the study population is similar to or better than that seen in many other lipid lowering studies. They suggest that results would have been even better if patient adherence had been better. In real patients, levels of non-adherence with therapy may be even higher than 42%.

There was a 24% further lowering of LDL-C when ezetimibe was combined with simvastatin vs simvastatin alone. At one year this was mirrored by significant further reductions in TC, triglycerides, non-high-density lipoprotein cholesterol, apolipoprotein B and high-sensity C-reactive protein in the simvastatin-ezetimibe group. Event rates for the primary end point at 7 years were 32.7% in the simvastastin-ezetimibe group and 34.7% in the simvastatin monotherapy group. (Absolute Risk Reduction (ARR): 2%. Hazard Ratio: 0.936). Rates of death from CV causes and any cause were similar in both groups. The rate of composite end point of death from CV causes, MI or stroke was significantly lower in the simvastatin-ezetimibe group.

PACEF Recommendations and Conclusions:

- **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.**
- **IMPROVE-IT contributes to the evidence base supporting the 'LDL hypothesis' i.e. the concept that excess LDL-C is a casual factor in the development of atherosclerotic vascular disease and that the reduction of LDL-C , regardless of the means, will result in a corresponding reduction in CV events. Considerable trial evidence now exists to back this up.**
- **A New England Journal of Medicine editorial argues that the results of IMPROVE-IT should not be interpreted as uniquely applying to ezetimibe; all reductions in LDL-C, regardless of mechanism, are likely to be equally beneficial.**
- **This study was undertaken prior to the advent of high intensity statin therapy, emerging safety concerns over simvastatin and the rise of generic atorvastatin. It does nothing to change the core recommendation that statin therapy at doses defined by the NICE Clinical Guideline is preferred first line.**
- **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.**

- **In response to IMPROVE-It, the following changes to Lincolnshire lipid modification guidance have been 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.**

References

Cannon Christopher P et al., 'Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes' *N Engl J Med 2015*; 372 2387-2397 (June 18 2015).
Jarcho John A and Kearney John F., 'Proof That Lower is Better – LDL Cholesterol and IMPROVE-IT', *N Engl J Med 2015*; 372 2448-2450 (June 18 2015).
NICE Clinical Guideline 181: *Lipid Modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease* (July 2014)
PACE Bulletin, Volume 8; Number 23, *Review of Lincolnshire Lipid Modification Guidance in Response to the NICE Clinical Guideline* (December 2014).

LINCOLNSHIRE PARTNERSHIP FOUNDATION TRUST *GUIDANCE ON THE USE OF ANTICONVULSANTS FOR MENTAL HEALTH PROBLEMS IN WOMEN OF CHILDBEARING POTENTIAL*

Sodium Valproate

- **Do not offer valproate for acute or long-term treatment of a mental health problem in women of childbearing potential.**
- If a woman is already taking valproate and is planning a pregnancy, advise her to gradually stop the drug because of the risk of foetal malformations and adverse neurodevelopment outcomes after any exposure in pregnancy.
- If a woman is already taking valproate and becomes pregnant, stop the drug because of the risk of foetal malformations and adverse neurodevelopmental outcomes.

Carbamazepine

- Do not offer carbamazepine to treat a mental health problem in women who are planning a pregnancy, pregnant or considering breastfeeding.
- If a woman is already taking carbamazepine and is planning a pregnancy or becomes pregnant, discuss with the woman the possibility of stopping the drug because of the risk of adverse drug interactions and foetal malformations.

Lamotrigine

- If a woman is taking lamotrigine during pregnancy, check lamotrigine levels frequently throughout the pregnancy and into the postnatal period as there can be a substantial variation in levels during this time.

REVIEW OF FORMULARY STATUS OF FIDAXOMICIN TABLETS (*DIFICLIR*) AND OTHER MICROBIOLOGIST LED ANTIBIOTICS FOR RESISTANT INFECTIONS

In close collaboration with Dr Bethan Stoddart, Consultant Microbiologist, ULH and in recognition of increasing problems with bacterial resistance in primary care, PACEF have reviewed the Formulary status of a number of microbiologist-led antibiotics and changed Lincolnshire recommendations as follows:

Drug	**Indication**	**Formulary status**
Cefixime 200mg tablets (*Suprax*)	For urinary tract infections.	Remains RED, for prescribing by Sexual Health only
Chloramphenicol 250mg capsules	Reserved for the treatment of life-threatening infections, particularly those caused by *Haemophilus influenza* and also typhoid fever	RED Included in the *Lincolnshire Joint Formulary* for these indications.
Fidaxomicin tablets 200mg (*Dificlir*)	For *C.difficile* infection	Moves from RED to AMBER (without shared care); can be prescribed by a GP subject to microbiologist advice.
Fosfomycin 3g sachets (unlicensed)	For use on the advice of a microbiologist for the treatment of uncomplicated lower urinary tract infections caused by multiple antibacterial resistant organisms when other antibacterials cannot be used	Moves from RED to AMBER (without shared care); can be prescribed by a GP subject to microbiologist advice and availability in primary care.
Linezolid 600mg tablets (*Zyvox*)	For nosocomial pneumonia, community acquired pneumonia and complicated SSTI in a hospital environment.	RED Included in the *Lincolnshire Joint Formulary* for these indications.
Vancomycin capsules 125mg and 250mg	For pseudomembranous colitis and staphylococcal enterocolitis	Moves from RED to AMBER (without shared care); can be prescribed by a GP subject to microbiologist advice.
Voriconazole 50mg and 200mg tablets (*Vfend*)	For the treatment of invasive aspergillosis, candidaemia in non-neutropenic patients, fluconazole resistant serious invasive Candida infections (including *C. krusei*), serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp in patients with progressive possibly life-threatening infections. Prophylaxis of invasive fungal infections in high risk allogeneic haematopoietic stem cell transplant recipients.	RED Included in the Lincolnshire Joint Formulary for these indications.

CHANGES TO GUIDANCE ON THE USE OF SGLT2 INHIBITORS

Janssen-Cilag Ltd have recently announced a reduction in the price of the 300mg strength of canagliflozin (*Invokana*) from £49.99 to £39.20 for 30 tablets which brings it into line with the cost of the 100mg strength tablets. The resulting price change now means that all three NICE approved sodium-glucose co-transporter 2 (SGLT2) inhibitors, dapagliflozin, canagliflozin and empagliflozin, cost the same for a 28 day course.

PACEF had previously been concerned at the significantly higher cost of the 300mg strength of canagliflozin compared to that of the 100mg strength, particularly as there was a lack of published information on the proportion of patients likely to need the higher dose. Previous PACEF guidance had therefore advised that either dapagliflozin or empagliflozin should be used first line based on the lower cost of treatment.

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	√ Dapagliflozin /metformin	X

	50mg/850mg & 50mg/1g (*Vokanamet*)	5mg/850mg & 5mg/1g (*Xigduo*)	
Dose range	100mg daily 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 pack	£39.20 (30 tabs) 100 and 300mg	£36.59 (28 tabs) 5 and 10mg	£36.59 (28 tabs) 10 and 20mg
Cost per month (28 days)	£36.59	£36.59	£36.59

PACEF recommendations

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.

Canagliflozin (*Invokana*) 100mg and 300mg tablets, dapagliflozin (*Forxiga*) 5mg and 10mg tablets and empagliflozin (*Jardiance*) 10mg and 20mg tablets are all recommended as treatment options when a SGLT2 inhibitor is indicated in combination with metformin and are designated as GREEN.

Canagliflozin and empagliflozin are also approved by NICE for triple therapy in combination with metformin and a sulfonylurea or metformin and pioglitazone.

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.

Currently both canagliflozin and dapagliflozin are also available as fixed dose combinations with metformin. The launch of a fixed dose combination of metformin with empagliflozin is expected imminently.

SUPPLY DIFFICULTIES WITH NAFTIDROFURYL 100MG CAPSULES NOW RESOLVED

Recent supply problems with naftidrofuryl 100mg capsules are now resolved restoring naftidrofuryl as the preferred treatment for intermittent claudication in people with peripheral arterial disease (PAD). Cilostazol (*Pletal*) is no longer PACEF approved for this condition.

Naftidrofuryl was approved for use by NICE in Technology Appraisal 223 for the treatment of intermittent claudication in people with peripheral arterial disease (PAD). In this capacity, it appears on the *Lincolnshire Joint Formulary* as the vasodilator of choice for this condition and is designated GREEN. All prescribing of naftidrofuryl should be generic.

Alternative treatments, such as cilostazol (*Plet*al), pentoxifylline (*Trental*) and inositol nicotinate (*Hexopal*/*Hexopal Forte*), are not approved by NICE and are designated RED-RED for this indication.

During a recent shortage of naftidrofuryl 100mg capsules, some secondary care specialists were advising that patients should be temporarily moved to cilostazol 50mg or 100mg

tablets. Now that naftidrofuryl supplies are restored, these patients should be moved back to naftidrofuryl 100mg capsules.

PACEF Recommendation:
Naftidrofuryl 100mg capsules are designated GREEN for the treatment of intermittent claudication in people with PAD. Alternative treatments, cilostazol (*Pleta*l), pentoxifylline (*Trental*) and inositol nicotinate (*Hexopal*/*Hexopal Forte*), are not approved by NICE and are designated RED-RED for this indication.

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

DENOSUMAB (*XGEVA, PROLIA*); INTRAVENOUS BISPHOSPHONATES: OSTEONECROSIS OF THE JAW — FURTHER MEASURES TO MINIMISE RISK

The MHRA have reiterated and strengthened guidance designed to mimimize the risk of patients on denosumab or bisphosphonates developing osteonecrosis of the jaw.
Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a known side effect of denosumab and bisphosphonates
To date, the MHRA has received 45 Yellow Card reports of ONJ in people taking denosumab (all doses) and 323 reports in people taking a bisphosphonate.
In patients treated for osteoporosis (regardless of route of administration), the risk of ONJ is small compared with that in patients treated with the higher doses used for cancer-related conditions. Other drug-specific risk factors for ONJ include drug potency (higher risk for highly potent compounds such as zoledronate, pamidronate and denosumab), route of administration (higher risk for parenteral administration) and cumulative dose.

Patient reminder cards and denosumab 120 mg contraindication
The MHRA and other EU medicines regulators have reviewed measures to minimise the risk of ONJ in patients taking denosumab or bisphosphonates. The review recommended introducing patient reminder cards for denosumab and intravenous bisphosphonates to inform patients of the risk and precautions to take before and during treatment. The review of ONJ and denosumab also recommended that denosumab 120 mg should be contraindicated in patients with unhealed lesions from dental or oral surgery.

Oral bisphosphonates: reminder of precautions to take
All bisphosphonates are associated with a risk of ONJ. Therefore, before prescribing oral bisphosphonates, patients should be advised to maintain good oral hygiene, attend routine dental check-ups and immediately report any oral symptoms such as dental mobility, pain, or swelling to a doctor and dentist.

Denosumab and intravenous bisphosphonates
Before prescribing denosumab or intravenous bisphosphonates:

- give patients the patient reminder card for their medicine
- explain the risk of osteonecrosis of the jaw and advise patients on precautions to take, for example:
    - inform their doctor if they have any problems with their mouth or teeth before starting treatment; if they wear dentures they should make sure their dentures fit properly before starting treatment.
    - maintain good oral hygiene and get routine dental check-ups during treatment
    - tell their doctor and dentist that they are receiving denosumab or an intravenous bisphosphonate if they need dental treatment or dental surgery.

    - tell their doctor and dentist immediately if they have any problems with their mouth or teeth during treatment (e.g. loose teeth, pain, swelling, non-healing sores or discharge).
- do not prescribe denosumab 120 mg (cancer indication) to patients with unhealed lesions from dental or oral surgery.

Continue to report suspected side effects to denosumab, bisphosphonates or any other medicines on a Yellow Card.

LATANOPROST (*XALATAN*): INCREASED REPORTING OF EYE IRRITATION SINCE REFORMULATION

The MHRA have highlighted increasing reports of eye irritation with latanoprost 50 microgram per ml eye drops (*Xalatan*) since reformulation. Prescribers are reminded that latanoprost 50 microgram per ml eye drops should always be prescribed generically and that the alternative second line treatment is travoprost 40microgram per ml (*Travatan*) or third line bimatoprost 100mcg per ml (*Lumigan*).

Xalatan is an eye-drop formulation of latanoprost. It is licensed for the reduction of intraocular pressure in adults and children with ocular hypertension and open angle glaucoma.

In 2013, the *Xalatan* pH was reduced from 6.7 to 6.0 to allow for long-term storage at room temperature. Following this reformulation, there have been an increasing number of reports of eye irritation from across the EU. The MHRA received no Yellow Card reports of eye irritation in people using *Xalatan* in the year before the reformulation, compared with 22 reports in the year after reformulation.

The MHRA advises when prescribing or dispensing the *Xalatan* brand of latanoprost:

- advise patients to tell their health professional if they experience severe eye irritation.
- review treatment if patient mentionc severe eye irritation.
- continue to report suspected side effects to latanoprost or any other medicines on a Yellow Card.

PACEF Comment:
PACEF prescribing guidance for chronic open angle glaucoma and ocular hypertension recommends latanoprost 50 microgram per ml eye drops as the prostaglandin analogue eye drop of first choice, particularly in those with early mild disease (see *PACE Bulletin* Vol 9 No 6 (May 2015)). Due to the comparatively high cost of the *Xalatan* brand compared to the generic, it should not be prescribed. All prescriptions for branded *Xalatan* should be reviewed with a view to transferring patients to generic latanoprost 50 microgram per ml eye drops. Second line options for those who have failed to achieve the desired reduction in IOP with latanoprost or who are unable to tolerate the product are either travoprost 40microgram per ml (*Travatan*) or third line for new patients bimatoprost 100mcg per ml (*Lumigan*).

COLPERMIN CAPSULES CONTAIN PEANUT OIL: AVOID IN PATIENTS WITH PEANUT ALLERGY

In a recent incident in Lincolnshire, a patient allergic to peanut/arachis oil was unwittingly prescribed peppermint oil capsules (*Colpermin*), a peanut/arachis oil containing preparation. Fortunately, the patient came to no harm.

On investigation it was found that *Colpermin* capsules were highlighted as containing peanut oil on *SystmOne* but only to those who chose to access the Drug Information screen. PACEF have taken steps to highlight the problem to SystmOne.

PACEF Recommendation;
Prescribers are alerted to the risk of peanut allergy sufferers being exposed to peanut/arachis oil as a constituent of peppermint oil capsules (*Colpermin*). Steps have been taken to ensure that this problem is flagged up to *SystmOne.*

NICE TECHNOLOGY APPRAISAL 338: *POMALIDOMIDE FOR RELAPSED AND REFRACTORY MULTIPLE MYELOMA PREVIOUSLY TREATED WITH LENALIDOMIDE AND BORTEZOMIB* (MARCH 2015)

- Pomalidomide, in combination with dexamethasone, is not recommended within its marketing authorisation for treating relapsed and refractory multiple myeloma in adults who have had at least 2 previous treatments, including lenalidomide and bortezomib, and whose disease has progressed on the last therapy.

PACEF Recommendation:
Pomalidomide 1mg, 2mg, 3mg and 4mg capsules (Imnovid) are designated RED- RED for this indication and are not approved for inclusion in the *Lincolnshire Joint Formulary.*

NICE TECHNOLOGY APPRAISAL 339: *OMALIZUMAB FOR PREVIOUSLY TREATED CHRONIC SPONTANEOUS URTICARIA* (JUNE 2015)

Omalizumab is recommended as an option for use as an add-on therapy for treating severe chronic spontaneous urticaria in adults and young people aged 12 years and over only if:

- the severity of the condition is assessed objectively, for example, using a weekly urticaria activity score of 28 or more.
- the person's condition has not responded to standard treatment with H1-antihistamines and leukotriene receptor antagonists.
- omalizumab is stopped at or before the fourth dose if the condition has not responded.
- omalizumab is stopped at the end of a course of treatment (6 doses) if the condition has responded, to establish whether the condition has gone into spontaneous remission, and is restarted only if the condition relapses.
- omalizumab is administered under the management of a secondary care specialist in dermatology, immunology or allergy.

PACEF Recommendation:
Omalizumab 150mg per ml solution for injection (*Xolair*) is designated RED for the management of chronic spontaneous urticaria and is approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. The marketing authorisation stipulates that treatment should only be initiated by physicians experienced in the diagnosis and treatment of severe persistent asthma or chronic spontaneous urticaria. As a result of this, omalizumab is unlikely to be initiated by ULH for this indication, but may be initiated from a specialist centre. Omalizumab is also licensed for use in patients (adults, adolescents and children (6 to <12 years of age) with convincing immunoglobulin E mediated asthma. It is approved by NICE for this indication and is already designated RED and included in the *Lincolnshire Joint Formulary* within this context.

NICE TECHNOLOGY APPRAISAL 340: *USTEKINUMAB FOR TREATING ACTIVE PSORIATIC ARTHRITIS* (JUNE 2015)

Ustekinumab is recommended as an option, alone or in combination with methotrexate, for treating active psoriatic arthritis in adults only when:

- treatment with tumour necrosis factor (TNF) alpha inhibitors is contraindicated but would otherwise be considered or
- the person has had treatment with 1 or more TNF–alpha inhibitors.

Ustekinumab treatment should be stopped if the person's psoriatic arthritis has not shown an adequate response using the Psoriatic Arthritis Response Criteria (PsARC) at 24 weeks. An adequate response is defined as an improvement in at least 2 of the 4 criteria (1 of which must be joint tenderness or swelling score), with no worsening in any of the 4 criteria. As recommended in NICE technology appraisal guidance on etanercept, infliximab and adalimumab for the treatment of psoriatic arthritis, people whose disease has a Psoriasis Area and Severity Index (PASI) 75 response but whose PsARC response does not justify continuing treatment should be assessed by a dermatologist to determine whether continuing treatment is appropriate on the basis of skin response.

PACEF Recommendation:
Ustekinumab injection (*Stelara*) is designated RED for this indication and approved for inclusion in the *Lincolnshire Joint Formulary.* The marketing authorisation stipulates that it is intended for use only under the guidance and supervision of a physician experienced in the diagnosis and treatment of psoriasis or psoriatic arthritis.

NICE TECHNOLOGY APPRAISAL 342: *VEDOLIZUMAB FOR TREATING MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS* (JUNE 2015)

Vedolizumab is recommended, within its marketing authorisation, as an option for treating moderately to severely active ulcerative colitis in adults only if the company provides vedolizumab with the discount agreed in the patient access scheme.

Vedolizumab should be given until it stops working or surgery is needed. At 12 months after the start of treatment, people should be reassessed to see whether treatment should continue. Treatment should only continue if there is clear evidence of ongoing clinical benefit. For people in complete remission at 12 months, consider stopping vedolizumab, resuming treatment if there is a relapse. People who continue vedolizumab should be reassessed at least every 12 months to see whether continued treatment is justified.

PACEF Recommendation:
Vedolizumab 300mg injection (*Entyvio*) is designated RED and approved for inclusion in the *Lincolnshire Joint Formulary* for the treatment of adult patients with moderately to severely active ulcerative colitis subject to NICE criteria. The license stipulates that treatment should be initiated and supervised by specialist healthcare professionals experienced in the diagnosis and treatment of ulcerative colitis. NICE have not yet appraised vedolizumab for the treatment of adult patients with moderately to severely active Crohn's disease and the drug remains RED-RED for this indication pending publication of NICE guidance.

NICE TECHNOLOGY APPRAISAL 347: *NINTEDANIB FOR PREVIOUSLY TREATED LOCALLY ADVANCED, METASTATIC, OR LOCALLY RECURRENT NON-SMALL-CELL LUNG CANCER* (JULY 2015)

Nintedanib in combination with docetaxel is recommended, within its marketing authorisation, as an option for treating locally advanced, metastatic or locally recurrent non-small-cell lung cancer of adenocarcinoma histology that has progressed after first-line chemotherapy, only if the company provides nintedanib with the discount agreed in the patient access scheme.

PACEF Recommendation:
Nintedanib (*Vargatef*) 100mg and 150mg capsules are designated RED and approved for inclusion in the *Lincolnshire Joint Formulary* for use in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy. There is another brand of nintedanib (*Ofev*) 100mg and 150mg capsules which has a UK marketing authorisation for use in adults for the treatment of Idiopathic Pulmonary Fibrosis (IPF). At present, this product remains RED-RED and is not approved for use on the *Lincolnshire Joint Formulary.*

NICE TECHNOLOGY APPRAISAL 348: *EVEROLIMUS FOR PREVENTING ORGAN REJECTION IN LIVER TRANSPLANTATION* (JULY 2015)

Everolimus is not recommended within its marketing authorisation for preventing organ rejection in people having a liver transplant.

PACEF Recommendation:
Everolimus (*Certican*) 0.25mg, 0.5mg and 0.75mg tablets are licensed for use in combination with tacrolimus and corticosteroids for prophylaxis of organ rejection in liver transplant patients. In accordance with NICE recommendations this product is designated RED-RED and is not approved for inclusion in the *Lincolnshire Joint Formulary.*

NICE TECHNOLOGY APPRAISAL 351: *CANGRELOR FOR REDUCING ATHEROTHROMBOTIC EVENTS IN PEOPLE UNDERGOING PERCUTANEOUS CORONARY INTERVENTION OR AWAITING SURGERY REQUIRING INTERRUPTION OF ANTI-PLATELET THERAPY* (TERMINATED APPRAISAL) (JULY 2015)

NICE is unable to make a recommendation about the use in the NHS of cangrelor for reducing atherothrombotic events in people undergoing percutaneous coronary intervention or awaiting surgery requiring interruption of anti-platelet therapy because no evidence submission was received from manufacturer.

PACEF Recommendation:
Cangrelor 50mg injection (*Kengrexal*) has recently been launched for co-administration with aspirin for the prevention of thrombotic events in adult patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) when an oral P2Y12 inhibitor has not been given and is not feasible or desirable. Following the termination of this NICE TA, cangrelor 50mg injection (*Kengrexal*) is designated RED-RED and is not approved for inclusion in the *Lincolnshire Joint Formulary.*

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