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 8; Number 10 **May 2014**

What's new this month?

- **Alogliptin (*Vipidia*) and alogliptin/metformin (*Vipdomet*) have been evaluated as non-inferior to other DPP-4 inhibitors (or gliptins) at a significantly lower cost. As a result of this, alogliptin 6.25mg, 12.5mg and 25mg tablets (*Vipidia*) and alogliptin/metformin 12.5mg/1g tablets (*Vipdomet*) are designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary* (see page 4).**
- **Tamsulosin 400 microgram/ solifenacin 6mg modified release tablets (*Vesomni*) are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary*. Where combination alpha blocker and antimuscarinic therapy is required for the treatment of moderate to severe storage and voiding symptoms in men with benign prostatic hyperplasia (BPH), lower cost generically available alternatives prescribed separately are preferred (see page 6).**
- **Where an oral liquid formulation of captopril is required, a licensed product is now available. Captopril oral solution 5mg in 5ml and 25mg in 5ml (*Noyada*) is designated AMBER without shared care and is available on a restricted basis through the *Lincolnshire Joint Formulary* for paediatric and existing stable adult patients only (see page 8).**
- **Colesevelam tablets 625mg (*Cholestagel*) are approved for unlicensed use in the second line treatment of symptoms associated with bile acid malabsorption, such as chronic diarrhoea or intractable pruritis. Prior to initiation of therapy, diagnosis of bile acid malabsorption must be confirmed by a specialist. As a result of this, colesevelam tablets 625mg (*Cholestagel*) are designated AMBER without shared care for this indication (see page 9).**

CONTENTS

pipette design; Combined hormonal contraceptives: risk of venous thromboembolism – clarification of advice

SUMMARY OF PACEF DECISIONS: *APRIL2014 UPDATE*

Drug	Indication(s)	Traffic Light Status
Alogliptin 6.25mg, 12.5mg and 25mg tablets *(Vipidia)*	For the management of type 2 diabetes mellitus in adults to improve glycaemic control in combination with other glucose lowering therapies, including insulin when these together with diet and exercise do not provide adequate glycaemic control.	GREEN Approved for inclusion on the *Lincolnshire Joint Formulary.*
Alogliptin/metformin 12.5mg/1g tablets *(Vipdomet)*	For the management of type 2 diabetes mellitus in adults: - as an adjunct to diet and exercise to improve glycaemic control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of alogliptin and metformin. - in combination with pioglitazone (i.e. triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and pioglitazone. - in combination with insulin (i.e. triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when insulin at a stable dose and metformin alone do not provide adequate glycaemic control.	GREEN Approved for inclusion on the *Lincolnshire Joint Formulary.*
Captopril oral solution 5mg in 5ml and 25mg in 5ml (*Noyada*)	For the treatment of: hypertension; congestive heart failure with reduction of systolic ventricular function, in combination with diuretics and, when appropriate digitalis and beta-blockers; short-term treatment following myocardial infarction (4 weeks); long-term prevention of symptomatic heart failure and type 1 diabetic nephropathy.	AMBER without shared care. Approved for inclusion on the *Lincolnshire Joint Formulary.* Approved for use as the preferred option when a liquid formulation of captopril is required.
Colesevelam tablets 625mg (*Cholestagel*)	Licensed as an adjunct to diet in patients with primary hypercholesterolemia who are not adequately controlled on a statin alone and as monotherapy as an adjunct to diet in patients with primary hypercholesterolemia in whom a statin is considered inappropriate or is not well tolerated.	RED-RED N.B. In exceptional circumstances maybe initiated by a specialist lipid clinic. Supply difficulties with colestyramine may necessitate wider use.
Colesevelam tablets 625mg (*Cholestagel*)	Unlicensed use for the treatment of chronic diarrhoea or intractable pruritis in patients with bile acid	AMBER without shared care. Approved for inclusion on the *Lincolnshire Joint* Formulary in a

	malabsorption	second line role after colestyramine for this indication.
Linagliptin 5mg tablets (*Trajenta*)	Licensed for the treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, or triple oral therapy in combination with a sulfonylurea plus metformin.	GREEN Second line DPP-4 inhibitor approved for use in patients with renal or hepatic impairment. Approved for inclusion on the *Lincolnshire Joint Formulary.*
Metolazone tablets 5mg and 10mg (unlicensed)	For use in patients with Chronic Kidney Disease who are resistant to loop diuretics alone.	AMBER without shared care. Approved for inclusion on the *Lincolnshire Joint Formulary.*
Sevelamer hydrochloride 800mg tablets (*Renagel*)	For hyperphosphataemia in patients on haemodialysis or peritoneal dialysis	RED-RED Removed from the *Lincolnshire Joint Formulary.* Existing patients can continue to be prescribed *Renagel.*
Sevelamer carbonate 800mg tablets (*Renvela*)	For hyperphosphataemia in patients on haemodialysis or peritoneal dialysis and patients with chronic kidney disease not on dialysis who have a serum phosphate concentration of 1.78mml/l or more.	AMBER with shared care Remains on the *Lincolnshire Joint Formulary.* New patients to be initiated on *Renvela.*
Saxagliptin 2.5mg and 5mg tablets (*Onglyza*)	Treatment of type 2 diabetes dual therapy in combination with metformin, sulfonylurea or thiazolidinedione (glitazone)	GREEN Under review pending publication of American Food and Drug Administration cardiovascular safety review. Approved for inclusion on the *Lincolnshire Joint Formulary.*
Sitagliptin 100mg tablets (*Januvia*)	Treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, sulfonlyurea or glitazone or triple oral therapy in combination with a sulphonylurea plus metformin or glitazone plus metformin or with insulin with or without metformin.	GREEN Fi rst line DPP-4 inhibitor of choice. Approved for inclusion on the *Lincolnshire Joint Formulary.*
Sitagliptin 50mg/metformin 1g (*Janumet*)	Treatment of type 2 diabetes as monotherapy when metformin is inappropriate due to contraindications or intolerance, dual therapy in combination with metformin, sulfonlyurea or glitazone or triple oral therapy in combination with a sulphonylurea plus metformin or glitazone plus metformin or with insulin with or without metformin.	GREEN First line DPP-4 inhibitor/ metformin combination product of choice. Approved for inclusion on the *Lincolnshire Joint Formulary.*
Strontium ranelate 2g sachets (*Protelos*)	For the treatment of postmenopausal osteoporosis and osteoporosis in men at increased risk of fracture	AMBER with shared care
Tamsulosin 400 microgram/ solifenacin 6mg modified release tablet *(Vesomni)*	For the treatment of moderate to severe urinary frequency, urgency and voiding symptoms associated with BPH where monotherapy is inadequate.	RED-RED. Not approved for inclusion in the *Lincolnshire Joint Formulary.*
Vildagliptin 50mg tablets (*Galvus*)	Treatment of type 2 diabetes dual therapy in combination with metformin, sulfonlyurea or glitazone.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*
Vildagliptin/metformin 50mg/850mg and 50mg/1g tablets (*Eucreas*)	Treatment of type 2 diabetes dual therapy in combination with metformin, sulfonlyurea or glitazone.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*

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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 NHS in Lincolnshire 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

NEW DRUG ASSESSMENT: *ALOGLIPTIN 6.25MG, 12.5MG AND 25MG (VIPIDIA) AND ALOGLIPTIN PLUS METFORMIN 12.5MG/1000MG TABLET (VIPDOMET)*

Alogliptin (*Vipidia*) and alogliptin/metformin (*Vipdomet*) have been evaluated as non-inferior to other DPP-4 inhibitors at a significantly lower cost.

Alogliptin (*Vipidia*) is the 5th dipeptidyl peptidase - 4 (DPP-4) inhibitor or gliptin to gain a UK marketing authorisation. It is authorised for the management of type 2 diabetes mellitus in adults to improve glycaemic control in combination with other glucose lowering therapies when these together with diet or exercise, do not provide adequate glycaemic control. As well as a single component therapy in a variety of strengths, there is also a combination product available: alogliptin/metformin 12.5mg/1000mg tablet (*Vipdomet*). Authorised indications support dual therapy with metformin, sulfonylurea or pioglitazone and triple therapy with pioglitazone and metformin. Although alogliptin is authorised for use with insulin (with or without metformin), it is not authorised as monotherapy or as triple therapy with metformin and a sulfonylurea. A comparison of all five DDP-4 inhibitors reveals that sitagliptin still has the widest range of authorised indications:

Indication	sitagliptin	saxagliptin	linagliptin	vildagliptin	alogliptin
Monotherapy	√	√	√	√	
Dual therapy					
with metformin	√	√	√	√	√
with sulfonylurea	√	√		√	√
with glitazone	√	√		√	√
Triple therapy					
with Sulfonylurea + metformin	√	√	√	√	
With glitazone + metformin	√				√
with insulin					
with insulin ± metformin	√	√	√	√	√

Supporting evidence comes from a series of clinical trials where alogliptin at a dose of 25mg demonstrated good glycaemic control in terms of reduction of HbA1c levels compared to placebo in combination with oral hypoglycaemic agents. A longer term efficacy and safety

trial undertaken over a period of two years demonstrated durability of control of the 25mg dose compared to glipizide treatment.

Alogliptin also comes to market with positive cardiovascular outcomes data; results from a 40 month study in type 2 diabetics showed non-inferiority compared to placebo in terms of rates of major cardiovascular events in a population of high risk patients who had experienced an acute coronary event in the 90 days prior to enrolment in the study. Saxagliptin is the only other DPP-4 inhibitor with cardiovascular outcome data, although a possible link between saxagliptin and increased risk of hospitalisation due to heart failure has prompted the American Food and Drug Administration (FDA) to request further clinical data from the manufacturer to fully assess this possible risk. No such concerns have arisen from the 40 month alogliptin cardiovascular safety study.

There is no comparative data between any of the DPP-4 inhibitors. Results from a systematic review comparing efficacy of DPP-4 inhibitors in terms of HbA1c reduction in combination with metformin suggest that alogliptin performs at least as well as other DPP-4 inhibitors. A recent assessment of the product by the Scottish Medicines Consortium (SMC) criticised this systematic review on the basis that some of the pivotal studies were excluded and that a wide range of variables between the studies made it difficult to draw definitive conclusions.

A cost comparison of the different DPP-4 inhibitors reveals that alogliptin (*Vipidia*) is currently the lowest cost agent:

Drug	**Dose**	**Cost (£) 28 days**
Alogliptin 25mg tablets (*Vipidia*) - Takeda	**25mg once daily**	**£26.60**
Alogliptin/ metformin 12.5mg/1g tablets (*Vipdomet*) – Takeda	**One twice daily**	**£26.60**
Linagliptin 5mg tablets (*Trajenta*) – Boehringer Ingelheim	5mg once daily	£33.26
Linagliptin/metformin 2.5mg/850mg tablets (*Jentadueto*) – Boehringer Ingelheim	One twice daily	£33.26
Linagliptin/metformin 2.5mg/1g tablets (*Jentadueto*) – Boehringer Ingelheim	One twice daily	£33.26
Saxagliptin 5mg tablets (*Onglyza*) – BMS/Astra Zeneca	5mg once daily	£31.60
Saxagliptin/metformin 2.5mg/850mg tablets (*Komboglyze*) – BMS/Astra Zeneca	2.5mg/850mg	£31.60
Saxagliptin/metformin 2.5mg/1g tablets (*Komboglyze*) – BMS/Astra Zeneca	2.5mg/1gram	£31.60
Sitagliptin 100mg tablets (*Januvia*) - MSD	100mg once daily	£33.26
Sitagliptin/metformin 50mg/ 1g tablets (*Janumet*) - MSD	One twice daily	£33.26
Vildagliptin 50mg tablet (*Galvus*) – Novartis	50mg twice daily	£31.76
Vildagliptin/metformin 50mg/850mg tablets (*Eucreas*) – Novartis	One twice daily	£31.71
Vildagliptin/metformin 50mg/1g tablets (*Eucreas*) – Novartis	One twice daily	£31.71

PACEF Recommendation:
PACEF currently endorse sitagliptin (*Januvia*) and saxagliptin (*Onglyza*) as the DPP-4 inhibitors of choice; designation: GREEN. Linagliptin (*Trajenta*) undergoes minimal elimination via the renal route and is the preferred option in patients suffering from renal or hepatic impairment; designation: GREEN. Alogliptin (*Vipidia*) and alogliptin/metformin (*Vipdomet*) have been evaluated as non-inferior to other DPP-4 inhibitors at a significantly lower cost. There is also cardiovascular outcomes data available for 40 months that shows non-inferiority to placebo in terms of rate of major cardiovascular events. As a result of this, alogliptin 6.25mg, 12.5mg and 25mg tablets (*Vipidia*) and alogliptin/metformin 12.5mg/1g tablets (*Vipdomet*) are designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary.* The place of saxagliptin in the *Lincolnshire Joint Formulary* is under review pending the results of the FDA cardiovascular safety review.

NEW DRUG ASSESSMENT: *TAMSULOSIN 400 MICROGRAM/SOLIFENACIN 6MG MODIFIED RELEASE TABLET (VESOMNI)*

Tamsulosin 400 microgram/ solifenacin 6mg modified release tablet (*Vesomni*) is a new combination product authorized for the treatment of moderate to severe storage symptoms (urgency, increased micturition frequency) and voiding symptoms associated with benign prostatic hyperplasia (BPH) in men not adequately responding to monotherapy.

PACEF reviewed three studies:

- SATURN, a phase 2 dose-finding study, showed no additional improvement in efficacy of combination tamsulosin/solifenacin therapy compared to tamsulosin monotherapy. A subsequent analysis of a sub-group of patients from this study with moderate to severe storage symptoms demonstrated improved efficacy of combination therapy over tamsulosin alone.
- NEPTUNE, a short-term (12 week) phase 3 study, compared the combination product to tamsulosin alone or placebo in males with moderate to severe storage symptoms; from this, combination therapy emerged as effective in improving symptom control in males with moderate to severe storage symptoms and was generally well tolerated.
- An open label extension of NEPTUNE demonstrated sustained efficacy and good tolerability over a period of up to 52 weeks.

PACEF published advice on the treatment of lower urinary tract symptoms (LUTS) in men in *PACE Bulletin* Volume 5 No 10 (May 2011). This was in response to NICE Clinical Guideline 97: *Lower urinary tract symptoms – the management of LUTS in men* (May 2010). In this guidance prescribers were advised to consider an antimuscarinic as well as an alpha blocker in men who still have storage symptoms after treatment with an alpha blocker alone. As there is no evidence of a clinically important difference in efficacy between the various antimuscarinic drugs, lower cost antimuscarinics are preferred first line, such as immediate release oxybutynin. Where there are tolerability issues with IR oxybutynin, the extended release product (*Lyrinel XL*) should be considered second line. Solifenacin (*Vesicare*), tolterodine (generic), trospium (*Regurin/Regurin XL*) or transdermal oxybutynin (*Kentara*) are all endorsed by NICE as possible second line alternatives**.**

Tamsulosin has been evaluated by PACEF and is the preferred alpha-blocker for use in elderly patients and those with a history of cardiovascular disease. Solifenacin is also an option on the *Lincolnshire Joint Formulary* if first line antimuscarinics are not tolerated or prove ineffective.

A cost comparison reveals the following:

Drug	**Daily dose**	**Cost (£) 30 days**
Tamsulosin 400 microgram/ solifenacin 6mg modified release tablet (*Vesomni*)	**One daily**	**£27.62**
Solifenacin 5mg tablets (*Vesicare*)	5mg once daily	£27.62
Solifenacin 10mg tablets (*Vesicare*)	10mg daily	£35.91
Tamsulosin 400 microgram sustained release tablets (*Flomaxtra XL*)	400mcg once daily	£10.47
Tamsulosin 400microgram modified release capsules (*Tabphyn MR*)	400mcg once daily	£4.28
Tamsulosin 400microgram modified release capsules (generic)	400mcg once daily	£5.04
Alternative alpha blockers		
Doxazosin 2mg tablets (generic)	2mg daily	£0.92
Doxazosin 4mg tablets (generic)	4mg daily	£1.10
Doxazosin 4mg modified release tablets (*Cardura XL*)	4mg daily	£5.35
Alfuzosin 2.5mg tablets (generic)	2.5mg two- three times daily	£4.30- £6.45
Alfuzosin 10mg modified release tablets (generic)	10mg once daily	£12.51
Alternative antimuscarinics		
Darifenacin 7.5mg tablets (*Emselex*)	7.5mg once daily	£27.30
Darifenacin 15mg tablets (*Emselex*)	15mg once daily	£27.30
Fesoterodine 4mg tablets (*Toviaz*)	4mg once daily	£27.62
Fesoterodine 8mg tablets (*Toviaz*)	8mg once daily	£27.62
Oxybutynin 5mg tablets (generic)	5mg 2-3 times daily	£2.90 - £4.35
Oxybutynin 5mg modified release tablets (*Lyrinel XL)*	5mg daily	£13.77
Oxybutynin 10mg modified release tablets (*Lyrinel XL*)	10mg daily	£27.54
Propiverine 15mg tablets (*Detrunorm*)	15mg 2-3 times daily	£19.28 - £28.92
Propiverine 30mg modified release capsules (*Detrunorm XL*)	One daily	£26.20
Tolterodine 2mg tablets	2mg twice daily	£3.28
Tolterodine 4mg sustained release capsules (*Detrusitol*	4mg daily	£27.62

XL)		
Tolterodine 4mg sustained release capsules (*Neditol*)	4mg daily	£13.81
Trospium chloride tablets 20mg (generic)	20mg twice daily	£25.21
Trospium chloride 60mg sustained release capsules (*Regurin XL*)	60mg once daily	£24.70

PACEF Recommendation:
PACEF and NICE guidance supports the use of combination antimuscarinic and alpha blocker use in men who still have storage symptoms after treatment with an alpha blocker alone. Lower cost generically available standard release antimuscarinics such as oxybutynin 5mg tablets and tolterodine 2mg tablets are preferred first and second line treatments. Where an alpha blocker is required concurrently, generic doxazosin 2mg or 4mg tablets or generic tamsulosin 400 microgram modified release capsules are recommended. Prescribing lower cost generically available components separately should ensure that first and second line treatment costs are kept below £10 per month. Most of the third line antimuscarinic agents, such as solifenacin, are revealed by the cost comparison to be premium price preparations and tamsulosin 400 microgram/ solifenacin 6mg modified release tablet (*Vesomni*) proves to be no exception. PACEF are concerned that the convenience of this single component once daily combination product will drive increasingly prominent use of solifenacin, a high cost, third line agent. As a result of this, tamsulosin 400 microgram/ solifenacin 6mg modified release tablets (*Vesomni*) are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary*. Where combination alpha blocker and antimuscarinic therapy is required, lower cost generically available components prescribed separately are preferred.

RAPID COST COMPARISON: *CAPTOPRIL ORAL SOLUTION 5MG IN 5ML AND 25MG IN 5ML (NOYADA)*

Captopril oral solution 5mg in 5ml and 25mg in 5ml (*Noyada*) is a newly licensed captopril liquid formulation. It holds a marketing authorisation for the treatment of:

- hypertension.
- congestive heart failure with reduction of systolic ventricular function, in combination with diuretics and, when appropriate digitalis and beta-blockers.
- short-term treatment following myocardial infarction (4 weeks).
- long-term prevention of symptomatic heart failure.
- type 1 diabetic nephropathy.

It is relatively expensive even compared to unlicensed liquid specials with the 5mg in 5ml costing £98.21 for 100ml and the 25mg in 5ml £108.94 for 100ml.

Existing guidance on the use of unlicensed specials in *PACE Bulletin* Volume 6 No 11 (September 2012) is amended as follows:

'Special order' product	Possible alternatives
Captopril liquid specials	The licensed product, captopril oral solution 5mg in 5ml and 25mg in 5ml (*Noyada*) is preferred. Where *Noyada* is unavailable, crushing or dispersing captopril 12.5mg, 25mg or 50mg tablets in water should be considered. Where all other alternatives are considered inappropriate, an unlicensed special could be prescribed as a last resort.

PACEF Recommendation:
Captopril oral solution 5mg in 5ml and 25mg in 5ml (*Noyada*) is the only liquid formulation of captopril to hold a marketing authorisation. It is approved for use as the preferred option when a liquid formulation of captopril is required; designation AMBER without shared care. It is approved for restricted use on the *Lincolnshire Joint Formulary* for paediatric and existing stable adult patients only.

RAPID DRUG ASSESSMENT: *METOLAZONE 5MG AND 10MG TABLETS (UNLICENSED)*

Metolazone is a quinazoline diuretic with properties similar to the thiazide diuretics. It inhibits sodium, chloride and water reabsorption at the distal convoluted tubule with a possible secondary mechanism of action in the proximal tubule. It was discontinued by the manufacturer in the UK in 2012 but continues to be available as an imported product.

Unlike thiazide diuretics which are of limited use, metolazone produces diuresis in patients with renal impairment and is particularly useful in patients with Chronic Kidney Disease who are resistant to loop diuretics alone.

PACEF Recommendation:
Metolazone 5mg and 10mg tablets are approved for re-introduction into the *Lincolnshire Joint Formulary* for patients with Chronic Kidney Disease who are resistant to loop diuretics alone. Designation: AMBER without shared care.

NEW INDICATION ASSESSMENT: *COLESEVELAM 625MG CAPSULES (CHOLESTAGEL) FOR THE TREATMENT OF BILE ACID MALABSORPTION*

Bile acid malabsorption is a cause of chronic diarrhoea. It can result from malabsorption secondary to gastro-intestinal disease or from a primary disorder associated with excessive bile acid production. Treatment with bile acid sequestrants, such as choestyramine (*Questran*), is often effective, but recent supply difficulties with *Questran* following a product recall in June 2013 has driven a search for alternatives. Among the alternatives identified have been:

- generic colestyramine, although supplies are limited. Cholestyramine (*Questran*) is the only bile acid sequestrant with a marketing authorisation that covers chronic diarrhoea.
- *Questran Light* is available but is less palatable than *Questran* and does not mix as easily with liquids; the formulation also contains aspartame which is unsuitable for some.
- Colesevelam 625mg capsules (*Cholestagel*)

Colesevelam (*Cholestagel*) holds a UK marketing authorisation for the treatment of hypercholesterolemia, but is not currently authorised for the treatment of bile acid malabsorption. Evidence supporting colesevelam for the treatment of chronic diarrhoea in patients with bile acid malabsorption comes from one small randomised controlled trial and two small case studies. The RCT was set up to assess the effect of colesevelam compared to placebo on gastrointestinal and colonic transit time, bowel function and colonic permeability in twenty four women with diarrhoea, predominantly caused by irritable bowel syndrome. Patients were randomised to receive either 1.875g of colesevelam or placebo twice daily for 12-14 days. Results showed longer gastric emptying times and better stool consistency in the colesevelam group, although none of these differences were statistically significant. In addition, only four patients within the already small trial population had documented evidence of bile acid malabsorption. As a consequence, the results of this trial were considered inconclusive and only marginally relevant to the patient group under discussion.

Two small case studies provided more convincing evidence. In a retrospective chart review of forty five people who had completed cancer treatment or were undergoing treatment for cancer who had had chronic symptoms of bile acid malabsorption for 23 months or more, colesevelam 1.25g three times a day was found to reduce diarrhoea, urgency to defecate, steatorrhea, frequency of defecation, abdominal pain and faecal incontinence. Another small case study in 5 patients with bile acid malabsorption showed an improvement in symptoms in patients prescribed colesevelam who could not tolerate colestyramine. Colesevelam also emerged as a well-tolerated treatment, with the most commonly reported adverse reactions being flatulence and constipation.

A cost comparison reveals that colesevelam (*Cholestagel*) is comparably priced with most other treatment options:

Product	Dose	Cost per pack	Cost £ (30 days)
Colesevelam tablets (*Cholestagel*)	625mg 2-6 tablets daily*.	£87.36 (180)	£43.68 - £87.36
Colestyramine sachets 4gram sugar free	3-6 sachets daily maximum 9 daily	£29.15 (50)	£52.47 - £104.94
Colestyramine 4 gram sachets *Questran*	3-6 sachets daily maximum 9 daily	£10.76 (50)	£19.37 -£38.74
Questran light	3-6 sachets daily maximum 9 daily	£16.15 (50)	£29.07 - £58.14
Colestipol sachets (*Colestid*)	5 gram** 1- 6 sachets daily.	£15.05 (30)	£45.15 - £90.30

PACEF Recommendation:

Following this review, colesevelam tablets 625mg (*Cholestagel*) are approved for the second line treatment of symptoms associated with bile acid malabsorption, such as chronic diarrhoea or intractable pruritis. Colestyramine remains the first line bile acid sequestrant of choice for the treatment of chronic diarrhoea; chlorphenamine remains the preferred first line option for intractable pruritis. Prior to initiation of therapy, diagnosis of bile acid malabsorption must be confirmed by a specialist. As a result of

this, colesevelam tablets 625mg (*Cholestagel*) are designated AMBER without shared care for this unlicensed indication. Colesevelam tablets 625mg (*Cholestagel*) remain RED-RED for primary hypercholesterolaemia (the authorised indication (see *PACE Bulletin* Vol 2 No 3 (April 2008)), although limited use as part of specialist lipid management in difficult cases is supported.

COLESEVELAM TABLETS (CHOLESTAGEL) CURRENT SUPPLY PROBLEMS

There have been recent reports of dispensing practices and community pharmacists experiencing difficulties in obtaining supplies of colesevelam. The manufacturer of the product and their main distributors Alliance Healthcare have confirmed that there is currently a shortage of this product with two of their wholesaler branches currently out of stock. Alliance Healthcare are proactively managing the current difficulties by co-ordinating all supplies through their emergency supply hotline. The number to call is 0203 044 8930. If the quantity that is requested seems to be large they are asking that a copy of the patient prescription is faxed to them for verification.

FORMULARY AMENDMENT: *SEVELAMER HYDROCHLORIDE 800MG TABLETS (RENAGEL) TO BE REMOVED FROM THE FORMULARY*

Currently both sevelamer hydrochloride 800mg tablets (*Renagel*) and sevelamer carbonate 800mg tablets (*Renvela*) are available on the *Lincolnshire Joint Formulary* and included in shared care guidelines for the management of hyperphosphataemia in adult patients receiving haemodialysis or peritoneal dialysis and for controlling hyperphosphataemia associated with chronic kidney disease (CKD). In order to avoid confusion, only the product preferred by Leicester Renal Unit is to be retained on the *Formulary*: sevelamer carbonate 800mg tablets (*Renvela*). Patient experience suggests that in general the carbonate formulation (*Renvela*) is better tolerated. Standardization will also help to reduce the risk of dispensing errors or queries when a salt or brand is not specified on the prescription. Both of the preparations are similarly priced.

PACEF Recommendation:
Sevelamer hydrochloride 800mg tablets (*Renagel*) are to be removed from the *Lincolnshire Joint Formulary* and re-designated RED–RED. Sevelamer carbonate 800mg tablets (*Renvela*) remain available and continue to be designated AMBER with shared care. Existing patients should remain on the product they are currently taking. New patients will be initiated on sevelamer carbonate 800mg tablets (*Renvela*).

SHARED CARE GUIDELINES: UPDATE

At the April 2014 PACEF meeting, the following shared care guidelines were approved for use:

- *Methylphenidate, atomoxetine, dexamfetamine and lisdexamfetamine in the management of Attention Deficit Hyperactivity Disorder (ADHD)*
- *Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease* (5th Edition)
- *Cinacalcet in the management of secondary hyperparathyroidism or parathyroid carcinoma*

Full text copies of all PACEF approved shared care guidelines are available through the PACEF section of the NHS in Lincolnshire website. Further information on all aspects of

shared care and interface related prescribing issues is available from Cathy Johnson, Interface Lead Pharmacist, Tel: (01205) 366273 ext 230 or email: cathy.johnson@gemcsu.nhs.uk

MEDICINES AND HEALTHCARE REGULATORY AGENCY: *DRUG SAFETY UPDATE* (MARCH 2014)

ORLISTAT: THEORETICAL INTERACTION WITH ANTIRETROVIRAL HIV MEDICINES

Orlistat may theoretically reduce the absorption of antiretroviral HIV medicines.

Advice for healthcare professionals:

- Initiate orlistat treatment only after careful consideration of the possible impact on efficacy of antiretroviral HIV medicines
- Pharmacists should advise people who take antiretroviral HIV medicines to consult their doctor before taking *Alli* (an over the counter brand of orlistat) in light of the possible interaction

ST JOHN'S WORT: INTERACTION WITH HORMONAL CONTRACEPTIVES, INCLUDING IMPLANTS – REDUCED CONTRACEPTIVE EFFECT

St John's wort interacts with hormonal contraceptives. This interaction reduces the effectiveness of contraception and increases the risk of unplanned pregnancy. This applies to all hormonal contraceptives except intrauterine devices, for which there are currently no data

Advice for healthcare professionals:

- Women taking hormonal contraceptives for pregnancy prevention should not to take herbal products containing St John's wort.

PACEF Comment:
All St John's wort preparations are classed as RED-RED by PACEF and should be neither prescribed nor recommended for purchase. This is due to variation in potency between different preparations and the serious risk of interaction with other medication.

STRONTIUM RANELATE: CARDIOVASCULAR RISK - RESTRICTED INDICATIONS AND NEW MONITORING REQUIREMENTS

The European Medicines Agency (EMA) has concluded its review of the risks and benefits of strontium ranelate (*Protelos*).

Advice for healthcare professionals:

- Strontium ranelate is now restricted to the treatment of severe osteoporosis in postmenopausal women and adult men at high risk of fracture who cannot use other osteoporosis treatments due to, for example, contraindications or intolerance

- Treatment should only be started by a physician with experience in the treatment of osteoporosis
- The risk of developing cardiovascular disease should be assessed before starting treatment. Treatment should not be started in people who have or have had:
    - ischaemic heart disease
    - peripheral arterial disease
    - cerebrovascular disease
    - uncontrolled hypertension
- Cardiovascular risk should be monitored every 6–12 months
- Treatment should be stopped if the individual develops ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease, or if hypertension is uncontrolled

PACEF Comment:
The April 2013 edition of the MHRA *Drug Safety Update* raised concerns on the cardiovascular risk of strontium ranelate and provided updated advice on the contraindications and cautions for this product. As a result of these PACEF advised that strontium ranelate granules *(Protelos*) were no longer considered appropriate for GP initiation and the product was reclassified as AMBER with shared care. New patients should only be initiated on strontium ranelate on the advice of a specialist with experience in the treatment of osteoporosis and within the context of a shared care guideline (SCG). A new Lincolnshire SCG is in development to support this. PACEF advice is that existing patients should be reviewed in accordance with MHRA guidance at their next routine appointment and consideration given to stopping therapy where a contra-indication is identified or where the risk of ongoing therapy is thought to outweigh the potential benefits.

METHYSERGIDE: SERIOUS FIBROTIC REACTIONS – RESTRICTED USE AND NEW MONITORING REQUIREMENTS

A Europe-wide review has concluded that there is a risk of fibrosis (mainly retroperitoneal fibrosis) associated with methysergide treatment. This side effect may be serious and in some cases irreversible or fatal.

Advice for healthcare professionals:

- Methysergide should only be used for prophylaxis of:
    - severe intractable migraine (with or without aura) with functional disability in adults when treatment with standard medicines has failed. Previous treatment must have included medicines of other classes for at least 4 months at the maximum tolerated dose
    - episodic and chronic cluster headache in adults when treatment with standard medicines has failed. Previous treatment must have included medicines of at least two classes for at least 2 months each
- Methysergide should no longer be used to treat diarrhoea caused by carcinoid disease
- Methysergide should only be started and supervised by specialised physicians with experience in the treatment of migraine and cluster headache
- People should be screened for fibrosis at the start of treatment and at least every 6 months thereafter. Screening must include heart ultrasonography, abdominal MRI,

and pulmonary function tests. Treatment must be discontinued if symptoms suggesting fibrosis occur unless an alternative cause is confirmed
- The continued need for methysergide treatment must be reassessed every 6 months using a treatment-free interval of at least 4 weeks between treatment courses

PACEF Recommendation
There is currently no prescribing of methysergide within Lincolnshire primary care. This drug is listed as a non-formulary drug due to safety concerns and is confirmed following this safety alert as RED-RED. It is not approved for use through the *Lincolnshire Joint Formulary*.

DORZOLAMIDE HYDROCHLORIDE/TIMOLOL MALEATE (COSOPT) PRESERVATIVE-FREE EYE DROPS: NEW PIPETTE DESIGN

In December 2013 we reported on eye injuries caused by the design of the pipette provided with *Cosopt* preservative-free eye drops. Because of these injuries, a new pipette design was introduced in February 2014 as an interim measure. The instructions for using the new design are enclosed in the product packaging. The old pipette design is now being withdrawn.

COMBINED HORMONAL CONTRACEPTIVES: RISK OF VENOUS THROMBO-EMBOLISM - CLARIFICATION OF ADVICE

The February 2014 edition of MHRA *Drug Safety Update* included an article about combined hormonal contraceptives (CHCs) and risk of venous thromboembolism (see *PACE Bulletin*, Vol 8 No 7 (April 2014)). This article refers to a letter that was sent to healthcare professionals through the Central Alerting System on Jan 22, 2014. Annexes 2–4 of the letter advise what contraception a woman should use instead of CHCs in the event of: major surgery; a period of prolonged immobilisation; or if she smokes and is older than 35 years.The annexes recommend that a non-hormonal form of contraception should be used in these situations; however, they ought to have stated that a different form of contraception should be used. This allows for use of progestogen-only contraception or non-hormonal contraception if desired.

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