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

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 10; Number 11 **August 2016**

What's new this month?

- **As future prescribing arrangements for gluten-free foods go under review in Lincolnshire, prescribers are asked to ensure that they are fully compliant with existing guidance. Specifically, non-staple foods such as sweet biscuits and cake mixes should not be prescribed as this is not consistent with healthy eating messages. In addition quantities ordered should be within Coeliac UK defined quantity guidelines (see page 4).**
- **Ivermectin 10mg/g cream (*Soolantra*) is approved for use for the treatment of moderate to severe papulo-pustular inflammatory lesions of rosacea. It should be considered second line in those for whom topical treatment is considered appropriate who have failed to respond sufficiently to either azelaic acid 15% gel (*Finacea*) or metronizole 0.75% gel or cream. Designation: GREEN (see page 5).**
- ***Octasa 400mg MR* and *800mg MR* tablets remain the 400mg and 800mg mesalazine MR formulations of choice on grounds of cost; ULH gastroenterologists have agreed to initiate *Octasa* in preference to *Asacol 400mg and 800mg MR* tablets in new patients (see pages 7-8).**
- ***Asacol 400mg and 800mg MR* tablets continue to be widely prescribed for existing patients, but are prohibitively expensive compared to equivalent *Octasa* formulations (see pages 7-8).**
- **Different mesalazine preparations cannot always be considered to be interchangeable. All prescribing of mesalazine preparations should clearly specify the brand name of the product prescribed. Prescribers are encouraged to review all patients currently taking mesalazine to ensure that future prescribing is brand specific (see pages 7 to 8).**
- **Mesalazine gastro-resistant sustained-release granules 500mg, 1g, 1.5g and 3g sachets (*Salofalk*) are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary*; in patients genuinely struggling to cope with the pill burden associated with treatment with MR tablets, mesalazine sustained-release granules in 1g, 2g and 4g sachets (*Pentasa Sachet*) are preferred (see pages 7 to 8).**
- **A new licensed formulation of fosfomycin 3g granules for oral solution has been approved for use as an alternative to the unlicensed alternative; designation AMBER. It should only be prescribed in primary care on the advice of a consultant microbiologist for the treatment of uncomplicated lower urinary tract infections caused by multiple antibacterial resistant organisms when other antibacterials cannot be used (see page 8).**
- **Both insulin lispro 100units/ml and 200units/ml (*Humalog*) are now approved for use through the *Lincolnshire Joint Formulary*, designation GREEN. The 200 units/ml strength is designed to reduce injection volume in those requiring daily doses in excess of 20 units (see page 9).**
- **Following review, apremilast 10mg, 20mg and 30mg tablets (*Otezla*) continue to be designated RED-RED for both psoriasis and psoriatic arthritis and are not approved for use through the *Lincolnshire Joint Formulary.* Individual Funding Requests for exceptional cases will continue to be considered through the usual IFR route (see page 10).**
- **Oxybutynin 2.5mg in 5ml and 5mg in 5ml oral solutions (Thame Laboratories Ltd) are prohibitively expensive and should only be prescribed as a last resort when dispersal**

of tablets in water (unlicensed use), oxybutynin 3.9mg/24 hours (*Kentera*) patches and even anticholinergic withdrawal have been fully considered. Subject to these restrictions oxybutynin 2.5mg in 5ml and 5mg in 5ml oral solutions are designated GREEN with the expectation that levels of usage will be very low (see page 11).

- **Sacubitril valsartan 49/51mg tablets and 97/103mg tablets (*Entresto*) are designated AMBER and approved for inclusion in the *Lincolnshire Joint Formulary* for the treatment of symptomatic chronic heart failure with reduced ejection fraction (see page 13).**
- **No shared care guideline is required, but, Lincolnshire *Guidance for Patients with Heart Failure with Reduced Ejection Fraction* has been developed collaboratively between PACEF and ULH Cardiology (see page 17).**

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SUMMARY OF PACEF DECISIONS: *JUNE 2016 UPDATE*

Device, Dressing or Drug	**Indication(s)**	**Traffic Light and *Joint Formulary* Status**
Apremilast 10mg, 20mg and 30mg tablets (*Otezla*) (Celgene)	For the treatment of moderate to severe chronic plaque psoriasis in adults who have failed to respond to, have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Apremilast 10mg, 20mg and 30mg tablets (*Otezla*) (Celgene)	For the treatment of active psoriatic arthritis in patients with an inadequate response or intolerance to DMARDs.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Cabazitaxel 60 mg concentrate and solvent for solution for infusion (*Jevtana*) (Sanofi)	For use in combination with prednisone or prednisolone, for the treatment of adult patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen.	RED Already approved for inclusion in the *Lincolnshire Joint Formulary* as part of the *New Cancer Drugs Fund*.
Fosfomycin 3g granules for oral solution (MercuryPharma)	For the treatment of uncomplicated lower urinary tract infections caused by multiple antibacterial resistant organisms when other antibacterials cannot be used	AMBER – should only be prescribed following a request from a consultant microbiologist. Replaces the unlicensed product on the *Lincolnshire Joint Formulary.*
Insulin lispro 200 units/ml *(Humalog Kwik Pen)* (Lilly)	For the treatment of diabetes mellitus when rapid acting insulin is required.	GREEN Approved for use through the *Lincolnshire Joint Formulary*.
Ivermectin 10mg/g cream (*Soolantra*) (Galderma)	For the topical treatment of inflammatory papulo-pustules of rosacea in adults.	GREEN **Second line in those for whom topical treatment is considered necessary who have failed to respond to topical azelaic acid 15% gel (*Finacea*) or**

		metronidazole 0.75% gel/cream. Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Mesalazine gastro-resistant modified release tablets 400mg and 800mg (*Asacol 400mg and 800mg MR Tablets*) (Allergan)	Mild to moderate acute exacerbations of ulcerative colitis. Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis	AMBER –should be initiated by a gastroenterologist. Shared care guideline not required. **Second line choice; *Octasa MR* 400mg or 800mg preferred.**
Mesalazine gastro-resistant modified release tablets 400mg and 800mg (*Octasa 400mg and 800mg MR Tablets*) (Tillotts)	Mild to moderate acute exacerbations of ulcerative colitis. Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis	AMBER –should be initiated by a gastroenterologist. Shared care guideline not required. **First line preferred choice.**
Mesalazine sustained-release granules in 1g, 2g and 4g sachets (*Pentasa Sachet*) (Ferring)	Mild to moderate acute exacerbations of ulcerative colitis. Maintenance of remission of ulcerative colitis and Crohn's ileo-colitis	AMBER –should be initiated by a gastroenterologist. Shared care guideline not required. **Consider in patients who struggle with the high pill burden associated with mesalazine MR tablets.**
Mesalazine gastro-resistant sustained-release granules in 500mg, 1g, 1.5g and 3g sachets (*Salofalk*) (Dr Falk)	For the treatment of acute episodes of ulcerative colitis, and maintenance of remission of ulcerative colitis.	RED-RED. Not approved for inclusion in the *Lincolnshire Joint Formulary.* Where a sustained release granule formulation of mesalazine is required *Pentasa Sachet* should be preferred.
Oxybutynin 2.5mg in 5ml and 5mg in 5ml oral solutions sugar-free (Thame Laboratories Ltd)	For urinary frequency, urgency and urge incontinence. Neurogenic bladder disorders. Nocturnal enuresis due to detrusor overactivity in children when other treatment has failed.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* where the patient is unable to swallow standard or sustained release oxybutynin tablets and dispersal of the 2.5mg and 5mg tablets in water (unlicensed use) and/or oxybutynin transdermal patch are considered to be inappropriate.
Oxybutynin 3.9mg/24 hours transdermal patch (*Kentera*) (Orion)	Urinary frequency, urgency and urge incontinence.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* where the patient is unable to swallow standard or sustained release oxybutynin tablets and dispersal of the 2.5mg and 5mg tablets in water (unlicensed use) is considered to be inappropriate. Not recommended for use in children.
Sacubitril valsartan 49/51mg tablets and 97/103mg tablets (*Entresto*) (Novartis)	For the treatment of symptomatic chronic heart failure with reduced ejection fraction.	AMBER without shared care. Should only be started by a heart failure specialist with access to a multi-disciplinary heart failure team. Subject to Lincolnshire *Guidance for the Treatment of Heart Failure with Reduced Ejection Fraction.*

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

GLUTEN FREE PRESCRIBING GUIDANCE: REMINDER

The prescribing of gluten-free (GF) foods is currently under review and, as part of the process, the Lincolnshire Clinical Commissioning Groups have asked PACEF to remind prescribers of existing guidance originally published in *PACE Bulletin* Volume 8 Number 3 (January 2014).

- Only patients with established gluten enteropathy (including coeliac disease, steatorrhoea due to gluten sensitivity and dermatitis herpetiformis) with or without coexisting wheat sensitivity should receive gluten free (GF) foods on prescription.
- The GF diet is potentially very restrictive and all patients should be referred to a dietitian for dietary assessment and advice as soon as possible after diagnosis. It is very important to ensure that the patient understands the diet and the complications which can occur due to poor compliance with it. As part of the dietary assessment, the patient will be provided with information on appropriate quantities to order based on Coeliac UK age and sex specific quantities guidance.
- PACEF are in support of the prescription of staple GF products for patients with an ACBS approved indication. Staple foods are defined as: bread, bread mixes, pasta, flour, pizza bases, breakfast cereals, crackers and crispbreads. Quantities prescribed should be tightly controlled within quantities defined in the Coeliac UK prescribing guide.
- In January 2011, Coeliac UK issued a statement confirming that they could not support the prescribing of non-staples such as sweet biscuits, cookies, cake mixes and cakes as the regular consumption of these foods is not consistent with healthy eating messages. As much as 10% of the volume of GF foods prescribed in Lincolnshire is for non-staple GF products (sweet biscuits, cookies, cake mixes etc). Regular review should ensure that prescribing of non-staple GF foods is kept to a minimum and only sanctioned in exceptional circumstances.

PACEF Comment
The number of non-staple GF products still available through Part XV (Borderline Substances) of the *Drug Tariff* is in decline. The products remaining are Barkat GF biscuits, GF bread and cake mix and GF digestive biscuits; Ener-G GF cookies (vanilla); Glutafin GF biscuits, GF digestive biscuits, GF shortbread biscuits, GF sweet biscuits (without chocolate or sultanas) and GF tea biscuits; and Juvela GF digestive biscuits, GF sweet biscuits and GF tea biscuits. All patients currently receiving prescriptions for any of these items should be reviewed with a view to stopping all prescribing of non-staple GF products.

- Patients should only receive GF products on prescription up to the recommended monthly quantity as designated in the Coeliac UK prescribing guide. Prescribers are urged to review all prescriptions for GF foods to ensure that patients cannot continue to order in quantities in excess of the Coeliac UK prescribing guide unless exceptional individual circumstances have been identified and agreed.

- Over-ordering of fresh GF bread can be extremely wasteful of NHS resources, particularly if surplus quantities go out of date and are wasted. Where fresh GF bread is prescribed, patients should be advised to freeze surplus quantities immediately upon receipt as fresh GF bread deteriorates rapidly if stored at room temperature. GF bread making at home can be a more cost-effective and palatable way of ensuring that GF bread is available in the home.
- Coeliac disease does not exempt individuals from prescription charges, although a pre-payment certificate (PPC) can reduce the cost of prescriptions. If an individual receives more than 4 prescription items in three months or 14 items in twelve months, a PPC can work out cheaper than single charges for each item.
- All prescribers are advised to refer to the Coeliac UK prescribing guideline *Gluten-free foods: a revised prescribing guide* (September 2013) for further information.

NEW DRUG ASSESSMENT: *IVERMECTIN 10MG/G CREAM (SOOLANTRA)*

Ivermectin 10mg/g cream (*Soolantra*) is approved for use for the treatment of moderate to severe papulo-pustular inflammatory lesions of rosacea. It should be considered second line in those for whom topical treatment is considered appropriate who have failed to respond sufficiently to either azelaic acid 15% gel (*Finacea*) or metronizole 0.75% gel or cream.

Ivermectin 10mg/g cream (*Soolantra*) is a new topical skin preparation licensed for the treatment of inflammatory papulo-pustules of rosacea in adults. It has both an anti-inflammatory and an anti-parasitic effect, causing the death of *Demodex* mites living on the surface of the skin that are now thought to be a contributory factor in skin inflammation.

Supporting evidence comes from two randomised controlled trials that compare the active product against placebo (vehicle cream) and a further comparative trial against metronidazole 0.75% cream. In these trials, ivermectin cream emerged as superior to placebo and metronidazole 0.75% cream as measured by improving rosacea severity scores and reduced inflammatory lesion count.

There is no comparative data against other commonly used topical treatments such as azelaic acid 15% gel (*Finacea*) and alternative oral therapies, such as doxycycline. Nor has concomitant use of ivermectin 10mg/g cream with other topical or systemic products been investigated.

Data from the long term extension phase of the two placebo controlled trials compared ivermectin with azelaic acid 15% gel used as a placebo replacement in the group of patients previously treated with placebo. Compared to azelaic acid, ivermectin was associated with a lower incidence of adverse effects.

Local adverse effects associated with ivermectin include skin burning sensation, skin irritation, pruritus and dry skin. These are mostly transient, mild to moderate in severity and usually decrease when treatment is continued. In the comparator trial versus metronidazole 0.75% gel, ivermectin appeared to be better tolerated than metronidazole gel.

Current treatment options for mild or moderate papulo-pustular rosacea (with a limited number of papules and pustules, and no plaques) include metronidazole 0.75% gel/cream and or azelaic acid 15% gel (*Finacea*). For moderate to severe papulo-pustular rosacea (with extensive papules, pustules, or plaques), oral tetracycline, erythromycin, doxycycline or lymecycline can be prescribed, although not all of these drugs are licensed for treating rosacea.

A cost comparison reveals the following:

Drug	Indication(s)	Daily dose range	Cost (£) per tube
Ivermectin 10mg/g cream (*Soolantra*) (Galderma)	For the topical treatment of inflammatory papulopustules of rosacea	Apply to whole face once daily for up to four months. Discontinue if no improvement after 3 months. Treatment course can be repeated.	£18.29 (1 x 30g)
Azelaic acid 15% gel (*Finacea*) (Bayer)	For the relief of mild to moderate papulopustular acne of the facial area and the topical treatment of papulopustular rosacea.	Apply to affected skin areas twice daily Discontinue if no improvement after 2 months.	£7.48 (1 x 30g)
Metronidazole 0.75% cream (prescribed generically reimbursed at *Rosex* price)	For the treatment of inflammatory papulo-pustules and erythema of rosacea	Thin layer applied to affected skin areas twice daily	£6.60 (1 x 30g) £9.88 (1 x 40g)
Metronidazole 0.75% gel (prescribed generically reimbursed at *Rosex* price)	For the treatment of inflammatory papulo-pustules and erythema of rosacea	Thin layer applied to affected skin areas twice daily	£6.60 (1 x 30g) £9.88 (1 x 40g)
Metronidazole 0.75% aqueous gel (*Acea*) (Ferndale)	For the treatment of acute inflammatory exacerbations of rosacea.	Apply twice daily for 8 weeks or longer.	£9.95 (1 x 40g)
Metrogel Metronidazole 0.75% aqueous gel (*Metrogel*) (Galderma)	For the treatment of acute inflammatory exacerbations of rosacea and for the deodorisation of malodorous fungating tumours	Apply twice daily for 12-16 weeks or longer if required.	£22.63 (1 x 40g)
Metronidazole 0.75% aqueous gel (*Metrosa*) (Linderma)	For the treatment of inflammatory papulopustules of rosacea.	Apply twice daily for 4 weeks; continue for a further 4 weeks if required.	£12.00 (1 x 30g) £19.90 (1 x 40g)
Metronidazole 0.75% cream (*Rosiced*)(Pierre Fabre)	For the topical treatment of inflammatory papulopustules of rosacea.	Apply twice daily for 6-12 weeks or longer if required.	£7.50 (1 x 30g)
Metronidazole 0.75% aqueous gel and cream (*Rozex*) (Galderma)	For the treatment of inflammatory papulo pustules and erythema of rosacea.	Apply twice daily for 12-16 weeks or longer.	£6.60 (1 x 30g) £9.88 (1 x 40g)
Brimonidine 3mg/g gel (*Mirvaso*) (Galderma).	For the symptomatic treatment of facial erythema due to rosacea.	Apply once daily until erythema subsides. Maximum dose 5mg per day.	£33.69 (1 x 30g)

Gram for gram, ivermectin 10mg/g cream is more than double the cost of azelaic acid and metronidazole preparations, but is only applied once daily compared to twice daily for the other products. As a result of this, a 30g tube is expected to last twice as long as twice daily alternatives and is more favourably priced in comparison than first appears.

PACEF Recommendations:
Ivermectin 10mg/g cream (*Soolantra*) is approved for use for moderate to severe papulo-pustular inflammatory lesions of rosacea; designation GREEN and approved for use through the *Lincolnshire Joint Formulary*. It should be reserved for second line use in those for whom topical treatment is considered necessary who have failed to respond to topical azelaic acid 15% gel (*Finacea*) and/or metronidazole 0.75% gel/cream. To minimise the cost of topical metronidazole it should either be prescribed generically as metronidazole 0.75% cream or gel or as *Rosex.*

NEW DRUG ASSESSMENT: *MESALAZINE GASTRO-RESISTANT GRANULES (SALOFALK)*

Mesalazine gastro-resistant sustained-release granules 500mg, 1g, 1.5g and 3g sachets (*Salofalk*) are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary*; in patients genuinely struggling to cope with the pill burden associated with treatment with MR tablets, mesalazine sustained-release granules in 1g, 2g and 4g sachets (*Pentasa Sachet*) are preferred.

Mesalazine gastro-resistant granules (*Salofalk*) are licensed for the treatment of acute episodes of ulcerative colitis and maintenance of remission of ulcerative colitis. The product is available in 500mg, 1g, 1.5g and 3g strengths. Sustained-release granule formulations of mesalazine such as *Salofalk* and *Pentasa* can be helpful in those patients who struggle with the high tablet burden associated with regular mesalazine treatment. There is no direct evidence comparing *Pentasa* sustained-release granules with *Salofalk* sustained-release granules.

A cost comparison confirms that the existing *Formulary* approved product *Pentasa* sustained release granules is lower cost than *Salofalk* sustained release granules at most doses.

Formulation	Dose	Cost
Sustained-release granules		
Mesalazine gastro-resistant sustained-release granules in 500mg, 1g, 1.5g and 3g sachets (*Salofalk*) (Dr Falk)	Acute episode of ulcerative colitis: 1.5g to 3g once daily or in 3 divided doses each day. Maintenance of remission of ulcerative colitis: 500mg three times a day or 3g once daily if high risk of relapse or adherence issues.	£18.90-£42.87 per month £18.90-£42.87 per month
Mesalazine sustained-release granules in 1g, 2g and 4g sachets (*Pentasa Sachet*) (Ferring)	Acute episode of ulcerative colitis: Up to 4 g once daily or in two to four divided doses. Maintenance of remission of ulcerative colitis: 2 g once daily.	Up to £22.95 per month. £22.95 per month.
Modified-release tablets		
Mesalazine gastro-resistant modified release tablets 400mg (*Octasa 400mg MR Tablets*) (Tillotts)	Acute episode of ulcerative colitis: Six tablets a day (2.4g) in divided doses. Maintenance of remission of ulcerative colitis: Three to six tablets a day (1.2g to 2.4g) in divided doses.	£36.40 per month £18.20 to £36.40 per month
Mesalazine gastro-resistant modified release tablets 400mg	Acute episode of ulcerative colitis: Six tablets a day (2.4g) in divided	£54.90 per month

(*Asacol 400mg MR Tablets*) (Allergan)	doses. Maintenance of remission of ulcerative colitis: Three to six tablets a day (1.2g to 2.4g) in divided doses.	 £27.45 to £54.90 per month
Mesalazine gastro-resistant modified release tablets 800mg (*Octasa 800mg MR Tablets*) (Tillotts)	Acute episode of ulcerative colitis: Three tablets a day (2.4g) in divided doses. Maintenance of remission of ulcerative colitis: Two to three tablets a day (1.6g to 2.4g) in divided doses.	£44.33 per month £29.55 to £44.33 per month
Mesalazine gastro-resistant modified release tablets 400mg (*Asacol 800mg MR Tablets*) (Allergan)	Acute episode of ulcerative colitis: Three tablets a day (2.4g) in divided doses. Maintenance of remission of ulcerative colitis: Maximum three tablets a day (2.4g) in divided doses.	£54.90 per month Up to £54.90 per month

PACEF Recommendations

PACEF undertook a comprehensive review of oral mesalazine in the treatment of inflammatory bowel disease in early 2013 and many of the conclusions continue to hold true (*PACE Bulletin* Vol 7 No 4 (February 2013)). Specifically:

- ***Octasa 400mg MR* and *800mg MR* tablets remain the 400mg and 800mg mesalazine MR formulations of choice on grounds of cost; ULH gastroenterologists have agreed to initiate *Octasa* in preference to *Asacol 400mg and 800mg MR* tablets in new patients.**
- ***Asacol 400mg and 800mg MR* tablets continue to be widely prescribed for existing patients, but are prohibitively expensive compared to equivalent *Octasa* formulations.**
- **Different mesalazine preparations cannot always be considered to be interchangeable. All prescribing of mesalazine preparations should clearly specify the brand name of the product prescribed. Prescribers are encouraged to review all patients currently taking mesalazine to ensure that future prescribing is brand specific.**

Following review of mesalazine sustained-release granules (*Salofalk*), PACEF has concluded that: (1) there is no evidence of any additional benefit from *Salofalk* over the equivalent *Pentasa* formulation and (2) at most doses *Salofalk* SR granules are higher cost than Pentasa SR granules. As a result of this, mesalazine gastro-resistant sustained-release granules 500mg, 1g, 1.5g and 3g sachets (*Salofalk*) are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary*; in patients genuinely struggling to cope with the pill burden associated with treatment with MR tablets, mesalazine sustained-release granules in 1g, 2g and 4g sachets (*Pentasa Sachet*) are preferred.

RAPID DRUG ASSESSMENT: *FOSFOMYCIN 3G GRANULES FOR ORAL SOLUTION*

A new licensed formulation of fosfomycin 3g granules for oral solution is approved for use as an alternative to the unlicensed alternative. It should only be prescribed in primary care on the advice of a consultant microbiologist for the treatment of

uncomplicated lower urinary tract infections caused by multiple antibacterial resistant organisms when other antibacterials cannot be used.

Fosfomycin trometamol is a broad spectrum antibiotic now available for the first time as a licensed oral preparation: fosfomycin 3g granules for oral solution. It is indicated for the treatment of acute uncomplicated lower urinary tract infections in adults, caused by pathogens sensitive to fosfomycin, and for periprocedural prophylaxis in diagnostic and surgical transurethral procedures.

Since September 2015, unlicensed fosfomycin 3g sachets have been approved for use through the *Lincolnshire Joint Formulary* for the treatment of uncomplicated lower urinary tract infections caused by multiple antibacterial resistant organisms when other antibacterials cannot be used. Fosfomycin 3g sachets are designated AMBER and can be prescribed only in response to a request from a microbiologist.

The standard adult dose for the treatment of uncomplicated lower urinary tract infections is one sachet (3g) taken on an empty stomach, either 1 hour before or at least 2 hours after meals and preferably before bedtime after emptying the bladder. The contents of a sachet should be dissolved in a glass of water and taken immediately after its preparation. For most patients with simple cystitis or lower UTI, a single dose should be sufficient, but, if there is evidence of ascending infection, further doses may be indicated.

The cost of the new licensed product is £75.45 for a single dose.

PACEF Recommendation:
Fosfomycin 3g granules for oral solution (MercuryPharma) are approved for use through the *Lincolnshire Joint Formulary*, designation AMBER, and should be prescribed preferentially over unlicensed alternative preparations. Fosfomycin should only be prescribed in primary care on the advice of a consultant microbiologist for the treatment of uncomplicated lower urinary tract infections caused by multiple antibacterial resistant organisms when other antibacterials cannot be used.

RAPID DRUG ASSESSMENT: *INSULIN LISPRO 200 IU/ML (HUMALOG KWIK PEN)*

Both insulin lispro 100 units/ml and 200 units/ml (*Humalog*) are now approved for use through the *Lincolnshire Joint Formulary*, designation GREEN. The 200 units/ml strength is designed to reduce injection volume in those requiring daily doses in excess of 20 units.

Insulin lispro (*Humalog*) is a rapid acting human insulin analogue. It is licensed for the treatment of diabetes mellitus when rapid acting insulin is required. It is normally administered shortly before meals, although it can also be given shortly afterwards.

Insulin lispro 100 units/ml (*Humalog*) is already available through the *Lincolnshire Joint Formulary* designation GREEN. The advantage of the 200 units/ml higher strength is that the same number of units can be delivered to the patient in half the injectable volume. As a safety feature, the maximum dose of insulin that can be delivered with *Humalog* insulin in a *KwikPen* device is 60 units irrespective of the strength of insulin used. If a patient requires doses in excess of 60 units they will have to have two injections; it must be stressed that it is very rare for a patient to require a dose of a rapid acting insulin in excess of 60 units.

In the Summary of Product Characteristics (SPC), the manufacture recommends that the higher strength of *Humalog* should only be used when the patient requires daily doses in excess of 20 units of rapid acting insulin.

Humalog 200units/ml is only available in a prefilled pen device, the *KwikPen*; this reduces the risk of confusion with the lower strength product which is available in cartridges, in a 10ml vial and in the *KwikPen* prefilled pen device. The different strengths of pen device are differentiated by different colour packaging.

A cost comparison reveals that *Humalog* insulin 200 units per ml is the same price unit for unit as the lower strength product.

PACEF Recommendation
Insulin lispro 200 units/ml (*Humalog*) is approved for inclusion in the *Lincolnshire Joint Formulary* designated GREEN. The 200 units/ml strength is designed to reduce injection volume in those requiring daily doses in excess of 20 units.

REVIEW: *APREMILAST (ORTEZLA) FOR THE TREATMENT OF PSORIASIS AND ACTIVE PSORIATIC ARTHRITIS*

PACEF were asked to review *Lincolnshire Joint Formulary* guidance on the use of apremilast (*Ortezla*) for psoriasis and active psoriatic arthritis (originally published in *PACE Bulletin* Vol 10 No 4 (February 2016)). Existing guidance is tabulated below:

NICE Technology Appraisal	Guidance	PACEF Recommendation
TA 368: *Apremilast for treating moderate to severe plaque psoriasis* (November 2015)	Apremilast is not recommended for treating adults with moderate to severe chronic plaque psoriasis that has not responded to systemic therapy, or where systemic therapy is contraindicated or not tolerated.	Apremilast 10mg, 20mg and 30mg tablets (*Otezla*) are designated RED-RED for this indication and have not been approved for use through the *Lincolnshire Joint Formulary.*
TA 372: *Apremilast for treating active psoriatic arthritis* (December 2015)	Apremilast alone or in combination with disease-modifying antirheumatic drug (DMARD) therapy is not recommended for treating adults with active psoriatic arthritis that has not responded to prior DMARD therapy, or where such therapy is not tolerated.	Apremilast 10mg, 20mg and 30mg tablets (*Otezla*) are designated RED-RED for this indication and have not been approved for use through the *Lincolnshire Joint Formulary.*

A proposal from ULH Dermatologists and Rheumatologists requested approval of apremilast for limited use in patients for whom a Tumour Necrosis Factor (TNF) inhibitor was either inappropriate or not tolerated or where the response was inadequate.

PACEF Recommendation
Current NICE guidance does not recommend apremilast for use for either of these licensed indications, even within a limited second or third line role. Pending NICE review of this position, PACEF declined this request. Apremilast 10mg, 20mg and 30mg tablets (*Otezla*) continue to be designated RED-RED for both psoriasis and psoriatic arthritis and are not approved for use through the *Lincolnshire Joint Formulary.* Individual Funding Requests for exceptional cases will continue to be considered through the usual IFR route.

RAPID COST COMPARISON: *OXYBUTYNIN 2.5MG IN 5ML/5MG IN 5ML ORAL SOLUTION SUGAR-FREE*

Oxybutynin 2.5mg in 5ml and 5mg in 5ml oral solutions are prohibitively expensive and should only be prescribed as a last resort when dispersal of tablets in water (unlicensed use), *Kentera* patches and even anticholinergic withdrawal have been fully considered.

Since the discontinuation of *Ditropan Liquid*, oxybutynin 2.5mg in 5ml and 5mg in 5ml oral solution (sugar free) has only been available as a licensed product from Thame Laboratories Ltd. A cost comparison illustrates the high cost of this product in comparison to low cost generic tablets and the *Kentara* patch:

Product	Dose	Cost (£)	Cost (£) (28 days treatment)
Oxybutynin 2.5mg tablets (generic)	2.5mg twice daily	£1.71 (56)	£1.71
Oxybutynin oral solution 2.5mg/5ml (Thame Laboratories Ltd)	2.5mg twice daily	£144.50 (150mls)	£269.73
Oxybutynin 5mg tablets (generic)	5mg twice daily	£2.14 (56)	£2.14
Oxybutynin oral solution 5mg/5ml (Thame Laboratories Ltd)	5mg twice daily	£199.20 (150mls)	£371.84
Oxybutynin 3.9mg/24 hours patch (Kentera) (Orion)	One patch twice weekly	£27.20 (8 patches)	£27.20

PACEF Recommendation

Oxybutynin 2.5mg in 5ml and 5mg in 5ml oral solution (Thame Laboratories Ltd) is extremely high cost in comparison to alternatives. For patients experiencing difficulties in swallowing the 2.5mg or 5mg tablets, consideration should be given to dispersing the tablets in water (unlicensed use). Alternatively, the oxybutynin 3.9mg/24 hour patch (*Kentera*) should be considered as a low cost alternative; designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary* where the patient is unable to swallow standard or sustained release oxybutynin tablets and dispersal of the 2.5mg and 5mg tablets in water (unlicensed use) is considered to be inappropriate. *Kentera* patches are not recommended for use in children. Only when all other options have been exhausted should oxybutynin 2.5mg in 5ml or 5mg in 5ml oral solution be prescribed. In the frail elderly and as part of end of life care, consideration should be given to withdrawal of anticholinergic medicines such as oxybutynin to reduce anticholinergic load and potentially improve the quality of life of the patient by removing disorientating anticholinergic side effects. Subject to these restrictions oxybutynin 2.5mg in 5ml and 5mg in 5ml oral solution (Thame Laboratories Ltd) are designated GREEN with the expectation that levels of usage will be very low.

NEW TRIAL ASSESSMENT: *EMPAGLIFLOZIN/EMPA-REG OUTCOME*

Reference: Bernard Zuinman, Christoph Warner, John M Lachin et al., *Empagliflozin, Cardiovascular Outcomes and Mortality in Type 2 Diabetes. N.Engl J Med* 2015; 373; 2117-2128 (Nov 26th 2015).

This study was designed to assess the effects of empagliflozin in addition to standard care on cardiovascular mortality in patients with type 2 diabetes. 7020 patients were randomly assigned to receive 10mg or 25mg empagliflozin or placebo once daily. Patients were

followed up for a median of 3.1 years. The main primary composite endpoint was death from cardiovascular causes, non-fatal myocardial infarction or nonfatal stroke. The key composite secondary endpoint was the primary endpoint plus hospitalisation rates for angina. Overall, patients with type 2 diabetes at high risk of cardiovascular events who received empagliflozin as compared with placebo had a lower rate of cardiovascular events and mortality from any cause when the study drug was added to standard care.

PACEF Comment

Published commentaries on the results of this trial have speculated on the possible mechanism of action for the observed reduction in cardiovascular events and all-cause mortality. Observation of the metabolic effects of Sodium Glucose Co-Transporter 2 inhibitors (SGLT2s) demonstrates that their use, as well as reducing HbA1c levels, also reduces body weight and blood pressure and increases HDL cholesterol. The most recent review published in the *Diabetes Care Journal* suggests that whilst metabolic effects may reduce the risk of cardiovascular disease, it is more likely that the combination of reduced BP and decreased extracellular volume is responsible for the reduction in CV mortality and heart failure hospitalisation.

A UKMI review of the same article highlights there are still questions to be answered regarding the mechanism of action of SGLT-2 inhibitors and, most importantly, whether this beneficial effect is a drug class effect or only seen with empagliflozin. There is consider interest in the cardiovascular effects of the newer diabetic treatments with a number of cardiovascular outcome studies already published or due to publish within the next couple of years. It is too soon to say whether any class of drug is beneficial or not in diabetic patients with known cardiovascular disease.

General advice remains to be vigilant with any of these new therapies in patients at risk of developing or worsening cardiovascular disease. Patients should report the development or worsening of symptoms suggestive of CVD to their doctor. There are other safety concerns emerging around the use of the SGLT2 inhibitors such as the association with diabetic ketoacidosis and potential higher risk of lower limb amputations.

NICE TECHNOLOGY APPRAISAL 391: *CABAZITAXEL FOR HORMONE-RELAPSED METASTATIC PROSTATE CANCER TREATED WITH DOCETAXEL* (MAY 2016)

NICE Technology Appraisal	Guidance	PACEF Recommendation
TA391 *Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel* (May 2016)	Cabazitaxel in combination with prednisone or prednisolone is recommended as an option for treating metastatic hormone-relapsed prostate cancer in people whose disease has progressed during or after docetaxel chemotherapy.	Cabazitaxel 60mg solution for infusion (*Jevtana*) is designated RED. Has already been approved for inclusion in the *Lincolnshire Joint Formulary* through the *New Cancer Drugs Fund.*

NICE TECHNOLOGY APPRAISAL 388: *SACUBITRIL VALSARTAN FOR TREATING SYMPTOMATIC CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION* (APRIL 2016)

Sacubitril valsartan 49/51mg tablets and 97/103mg tablets (*Entresto*) are designated AMBER and approved for inclusion in the *Lincolnshire Joint Formulary* for the treatment of symptomatic chronic heart failure with reduced ejection fraction.

NICE Recommendations are as follows:

1.1 Sacubitril valsartan (*Entresto*) is recommended as an option for treating symptomatic chronic heart failure with reduced ejection fraction, only in people:
(1) with New York Heart Association (NYHA) class II to IV symptoms and
(2) with a left ventricular ejection fraction of 35% or less and
(3) who are already taking a stable dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor-blockers (ARBs).
1.2 Treatment with sacubitril valsartan should be **started by a heart failure specialist with access to a multidisciplinary heart failure team**. Dose titration and monitoring should be performed by the most appropriate team member as defined in NICE's guideline on chronic heart failure in adults: management.

The NICE Appraisal Committee concluded that sacubitril valsartan should only be offered to patients in place of ACEIs or ARBs, who are symptomatic despite already taking a stable dose of ACEIs or ARBs.

Marketing authorisation

- Sacubitril valsartan (*Entresto*) has a UK marketing authorisation for:
  'the treatment of symptomatic chronic heart failure with reduced ejection fraction.'
- Sacubitril valsartan is an angiotensin receptor neprilysin inhibitor (ARNI), including sacubitril (a neprilysin inhibitor) and valsartan (an angiotensin II receptor blocker). Both sacubitril and valsartan lower blood pressure.
- The inhibition of neprilysin is a novel development in the management of heart failure.

Dose

- The recommended starting dose is one 49/51mg tablet twice daily (48.6mg sacubitril/51.4mg valsartan). The dose should be doubled at 2 to 4 weeks to a target dose of one 97/103mg tablet twice daily as tolerated by the patient (97.2mg sacubitril/102.8mg valsartan). **There is a need for upward dose titration and monitoring.**

Specialist and GP responsibilities

- **The specialist heart failure service will be responsible for initiation of sacubitril valsartan, dose titration over 2 to 4 weeks and renal monitoring during the initiation/titration period.**
- **GPs will be responsible for ongoing prescribing of sacubitril valsartan after initiation/titration and regular 6 monthly monitoring of U&Es; renal function will need to be monitored more frequently in those with poor renal function or in those suffering from conditions that may induce dehydration or change renal function (e.g. diarrhoea and vomiting).**

Adverse reactions

- Hypotension, hyperkalaemia and renal impairment.
- Generally in line with other products acting on the renin angiotensin system. The overall safety profile is comparable to enalapril. Sacubitril valsartan is associated with higher rates of hypotension due to a greater vasodilator effect. It is associated with a lower incidence of renal impairment and renal failure. Enalapril is associated with higher rates of hyperkalaemia, cardiac failure, cough, dyspnoea, hypertension, hyperuricemia and constipation.

Trial Evidence

PARADIGM-HF trial

- A randomised, double-blind, controlled, phase III trial comparing sacubitril valsartan with enalapril.
- Both treatments were used in combination with standard care (e.g. beta-blockers, aldosterone antagonists).
- The trial included people with symptomatic heart failure (NYHA Class II to IV) with left ventricular ejection fraction (LVEF) of 35% or lower.
- Enalapril was chosen as the comparator ACEI as it had been most widely studied in this population.
- Eligible patients were already on an ACEI or ARB equivalent to enalapril 10mg per day for 4 weeks or more before screening.
- Eligible patients were switched to enalapril 10mg twice daily for a two week enalapril run-in period.
- Sacubitril valsartan run-in (4 to 6 weeks): sacubitril valsartan 100mg twice daily increased to 200mg twice daily
- Patients with no unacceptable side effects during the run-in periods were randomly assigned to either sacubitril valsartan (200mg twice daily) or enalapril (10mg twice daily).
- At baseline, 93% of patients were taking a BB and 56% an aldosterone antagonist.
- The primary end point was a composite of death from cardiovascular cause or a first hospitalisation for worsening heart failure. Significantly favoured sacubitril valsartan.
- The secondary outcomes were all-cause mortality and change from baseline to 8 months in the Kansas City Cardiomyopathy Questionnaire.
- Sacubitril valsartan showed a significantly reduced risk for all-cause mortality and all cause hospitalization. It also performed better than enalapril on the KCCQ assessment.

The NICE Appraisal Committee concluded that, for the population included in the PARADIGM-HF trial, sacubitril valsartan was statistically significantly more clinically effective than enalapril at reducing hospitalisations and improving overall mortality and CV mortality. They also concluded that the results of PARADIGM-HF were relevant to routine clinical practice in England.

Meta-analysis

- Sacubitril valsartan was compared to angiotensin 2 receptor antagonists for patients who could not have an ACEI. This was performed in order to inform the economic model presented to NICE as there is no head-to-head evidence comparing sacubitril valsartan with any of the ARBs.

- The MA included 28 RCTs.
- Conclusions were: (1) ARBs and ACEIs are broadly equivalent; (2) sacubitril valsartan was superior to ARBs in terms of all-cause and CV mortality and broadly equivalent in terms of all-cause hospitalisation; (3) sacubitril valsartan was superior to ACEIs in terms of all-cause and CV mortality and superior in terms of all-cause hospitalisation.

TITRATION Trial

- This was a multicentre, randomised, double-blind, parallel group, phase II study in clinically stable outpatients or hospitalised patients that evaluated the safety and tolerability of sacubitril valsartan at increasing doses.

Cost-effectiveness

Cost Comparison

Drug	Dose	Cost 28 days
Sacubitril valsartan 49/51mg tablets (containing 48.6mg sacubitril/51.4mg valsartan) (*Entresto*) (Novartis)	One tablet twice daily	£91.56
Sacubitril valsartan 97/103mg tablets (containing 97.2mg sacubitril/102.8mg valsartan) (*Entresto*) (Novartis)	One tablet twice daily	£91.56
Valsartan 40mg capsules (generic)	One tablet twice daily	£3.00
Valsartan 80mg capsules (generic)	One tablet twice daily	£2.98
Valsartan 40mg capsules (*Diovan*) (Novartis)	One tablet twice daily	£27.94
Valsartan 80mg capsules (*Diovan*) (Novartis)	One tablet twice daily	£27.94

The NICE Appraisal Committee concluded that the most plausible ICERs for sacubitril valsartan were between £26,000 and £30,000 per QALY gained. This is just below the upper cost-effectiveness threshold of £30,000 and leads to the conclusion that sacubitril valsartan is a cost-effective use of NHS resources. In terms of cost, sacubitril valsartan is 30 times the cost of generic valsartan. The NICE Cost Model predicts that Lincolnshire primary care prescribing costs of sacubitril valsartan will reach £1 million over 5 years.

PACEF Recommendation;

Sacubitril valsartan 49/51mg tablets and 97/103mg tablets (*Entresto*) are designated AMBER and approved for inclusion in the *Lincolnshire Joint Formulary*. No shared care guideline is required, but, Lincolnshire *Guidance for Patients with Heart Failure with Reduced Ejection Fraction* has been developed collaboratively between PACEF and ULH Cardiology (see below). Sacubitril valsartan will only be offered to patients who are symptomatic despite already taking a stable dose of an ACEI or ARB. Treatment with sacubitril valsartan will be initiated and dose titrated by a heart failure specialist with access to a multidisciplinary heart failure team. The specialist heart failure service will be responsible for initiation of sacubitril valsartan, dose titration over 2 to 4 weeks and renal monitoring during the initiation/titration period. GPs will be responsible for ongoing prescribing of sacubitril valsartan after initiation/titration and regular 6 monthly monitoring of U&Es; renal function will need to be monitored more frequently in those with poor renal function or in those suffering from

conditions that may induce dehydration or change renal function (e.g. diarrhoea and vomiting).

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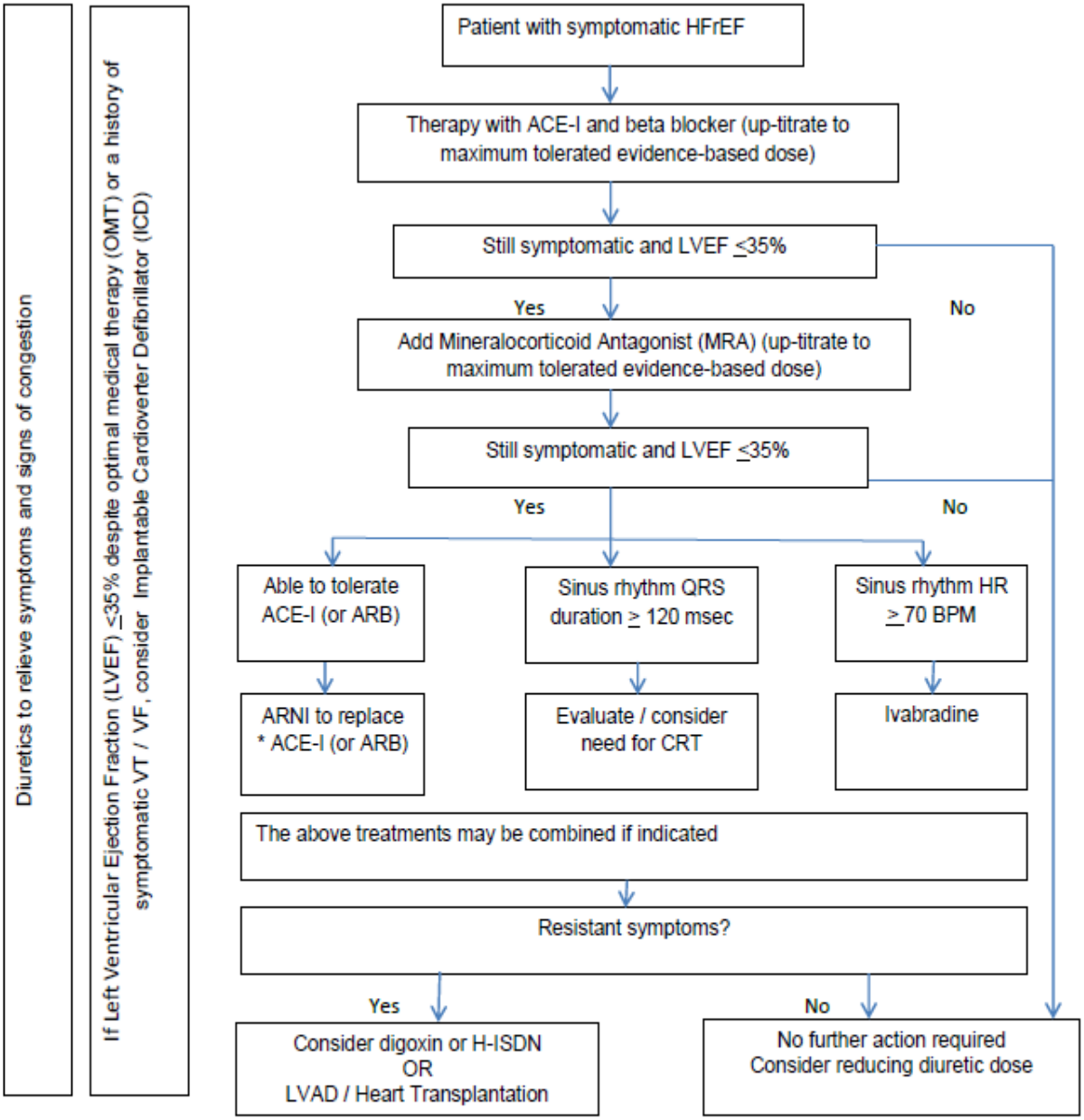
August 2016

Lincolnshire Guidance for Patients with Heart Failure and Reduced Ejection Fraction (HFrEF)



Notes *Switching of ACE-I / ARB to ARNI can only be initiated following cardiology specialist review. When a patient is switched from an ACE-I (or ARB) to an ARNI, the Heart Failure Service at ULHT will organise for physical review that will include renal monitoring during the period of the switching process. If the patient is under the care of the Community Heart Failure Team they will organise the switching process for their patients.

Stable patients on an ACE-I / ARB / ARNI / MRA should have their U&E's checked by their primary care physician no less than 6 monthly and more often if known to have poor renal function or suffering from conditions that may induce dehydration or change renal function (i.e. D&V).