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 12 **July 2015**

What's new this month?

- ***Sirdupla* is a new generic salmeterol/fluticasone propionate combination metered dose inhaler (MDI) launched by Mylan as a lower cost alternative to *Seretide 125* and *250 Evohaler.* Both *Sirdupla* 25/125 MDI and *Sirdupla* 25/250 MDI are designated GREEN and approved for use on the *Lincolnshire Joint Formulary*. Prescribers are urged to review all adult patients currently prescribed *Seretide 125 Evohaler* or *Seretide 250 Evohaler* with a view to switching patients to the equivalent strength *Sirdupla* MDI. In order to ensure that the NHS pays for the lower cost *Sirdupla* product rather than the originator brand *Seretide Evohaler*, prescribers are asked to ensure that Sirdupla is always prescribed by brand. All three strengths of the *Seretide Evohaler* (50, 125 and 250) remain available on the *Lincolnshire Joint Formulary* designation GREEN, primarily for use in children. *Sirdupla* 25/125 MDI and 25/250 MDI are only licensed for use in adult patients (see page 4).**
- **Budesonide 3mg gastro-resistant capsules (*Budenofalk*) are designated AMBER without shared care and preferred first line for the induction of remission in patients with mild to moderate Crohn's disease as they are lower cost than alternatives; they are approved for inclusion in the *Lincolnshire Joint Formulary* for this indication (see page 5).**
- **Budesonide 3mg gastro-resistant sustained release capsules (*Entocort CR*) are designated AMBER without shared care and recommended second line for the same indication; they are already included in the *Lincolnshire Joint Formulary*. Advice from local gastroenterologists is that budesonide products available in the 3mg strength are preferred as this allows for dose adjustment and for doses to be gradually tailed off. In order to ensure continuation of supply it is recommended that these products are prescribed by brand (see page 5).**
- **Budesonide 9mg gastro-resistant granules (*Budenofalk Granules*) and budesonide 9mg sustained release gastro-resistant tablets (*Cortiment*) are designated RED-RED and should not be prescribed (see page 5).**
- **There are now a number of macrogol containing laxatives available that are significantly lower cost than the originator brand, *Movicol*. Prescribers are advised to use a lower cost brand wherever a macrogol containing laxative is indicated. For adults, the elderly and adolescents the following products are designated GREEN and approved for use on the *Lincolnshire Joint Formulary*: Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*CosmoCol*); Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes powder for oral solution (*CosmoCol Half*); Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Laxido Orange*); and Macrogol (polyethylene glycol) 3350 13.125g pluselectrolytes powder for oral solution (*Molaxole*). For children, Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes, powder for oral solution (*CosmoCol* Paediatric). In order to ensure that the preferred product is supplied, these products should be prescribed by brand name. The *Movico*l range of products are higher cost in comparison to equivalent preparations and should no longer be prescribed. *Movicol, Movicol-Half* and *Movicol Paediatric* are designated RED-RED and have been removed from the *Lincolnshire Joint Formulary* (see page 6).**

- **Sodium hyaluronate 1% 1.2ml peri-articular injection pre-filled syringe (*SportVis* and *TendoVis*) are not recommended for use and are designated RED-RED. They have not been approved for inclusion in the *Lincolnshire Joint Formulary* (see page 9).**
- ***Lecicarbon C*, a new suppository formulation for constipation in children, is designated RED-RED and is not approved for inclusion in the *Lincolnshire Joint Formulary* (see page 9).**
- **The MHRA has highlighted the risk of diabetic ketoacidosis associated with the SGLT2 inhibitors, canagliflozin, dapagliflozin and empagliflozin (see page 10).**
- **The MHRA have published advice to prescribers on the small increased cardiovascular risk associated with high-dose ibuprofen (≥ 2400mg/day). They also review the evidence base behind the potential interaction between ibuprofen and low-dose aspirin (see page 11).**
- **The MHRA have published information on the risk of uterine perforation linked to insertion of an intra-uterine contraceptive device or intra-uterine system (see page 12).**

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SUMMARY OF PACEF DECISIONS: *JUNE/JULY 2015 UPDATE*

Drug	Indication(s)	Traffic Light and *Joint Formulary* Status
Budesonide 3mg gastro-resistant capsules (*Budenofalk*) (Dr Falk)	For the induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon. For the symptomatic relief of chronic diarrhoea due to collagenous colitis. For autoimmune hepatitis.	AMBER without shared care – first line. Included in the *Lincolnshire Joint Formulary*
Budesonide 9mg gastro-resistant granules (*Budenofalk Granules*) (Dr Falk)	For the induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon. For the symptomatic relief of chronic diarrhoea due to collagenous colitis.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary.*
Budesonide 3mg gastro-resistant sustained release capsules (*Entocort CR*) (AstraZeneca)	For the induction of remission in patients with mild to moderate Crohn's disease affecting the ileum and/or the ascending colon.	AMBER without shared care – second line after *Budenofalk*. Included in the *Lincolnshire Joint Formulary*
Budesonide 9mg sustained release gastro-resistant tablets (*Cortiment*) (Ferring)	For the induction of remission in mild to moderate active ulcerative colitis, where mesalazine is not sufficient.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary.*
Lecicarbon C suppositories (containing sodium hydrogen carbonate 250mg and sodium dihydrogen phosphate 340mg per suppository) (Aspire Pharma)	For constipation, bowel clearance and diagnostic procedures in children under 12 years	RED-RED. Not approved for inclusion in the *Lincolnshire Joint Formulary*.
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*

(*CosmoCol*) (Stirling Anglian)	children under 12 years.	
Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes powder for oral solution (*CosmoCol Half*) (Stirling Anglian)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*
Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes, powder for oral solution (*CosmoCol Paediatric*) (Stirling Anglian)	For the treatment of chronic constipation in children aged from 2 to 11 years. For resolving faecal impaction in children aged 5 years and over.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Laxido Orange*) (Galen)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.	GREEN Included in the *Lincolnshire Joint Formulary*
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Molaxole*) (Meda)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.	GREEN Included in the *Lincolnshire Joint Formulary*
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Movicol*) (Norgine)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.	RED-RED No longer included in the *Lincolnshire Joint Formulary*.
Macrogol (polyethylene glycol) 3350 6.563g plus electrolytes powder for oral solution (*Movicol-Half)* (Norgine)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.	RED-RED No longer included in the *Lincolnshire Joint Formulary*.
Macrogol (polyethylene glycol) 3350 6.563g plus electrolytes, powder for oral solution (*Movicol Paediatric*) (Stirling Anglian)	For the treatment of chronic constipation in children aged from 2 to 11 years. For resolving faecal impaction in children aged 5 years and over.	RED-RED No longer included in the *Lincolnshire Joint Formulary*.
Salmeterol and fluticasone propionate 25mcg/125mcg and 25mcg/250mcg metered dose inhaler (*Sirdupla*) (Mylan)	For the regular treatment of asthma in adults where use of a long-acting β2 agonist (LABA) and inhaled corticosteroid (ICS) in combination is appropriate. Can be used in patients over 18 not adequately controlled with an 'as needed' inhaled short-acting β2 agonist and an ICS and in those already controlled on LABA/ICS combination therapy.	GREEN Included in the *Lincolnshire Joint Formulary.* First line preferred product in adult patients,
Salmeterol and fluticasone propionate 25mcg/50mcg metered dose inhaler (*Seretide 50 Evohaler*) (A&H)	For the regular treatment of asthma in adults and children over 5 years where use of a long-acting β2 agonist (LABA) and inhaled corticosteroid (ICS) in combination is appropriate. Can be used in patients not adequately controlled with an 'as needed' inhaled short-acting β2 agonist and an ICS and in those already controlled on LABA/ICS combination therapy.	GREEN Included in the *Lincolnshire Joint Formulary.* *Licensed for children over 5 years.* *Sirdupla* MDI is the preferred product in adult patients,
Salmeterol and fluticasone propionate 25mcg/125mcg and 25mcg/250mcg metered dose inhaler (*Seretide 125* and *250 Evohaler*) (A&H)	For the regular treatment of asthma in adults where use of a long-acting β2 agonist (LABA) and inhaled corticosteroid (ICS) in combination is appropriate. Can be used in patients not adequately controlled with an 'as needed' inhaled short-acting β2 agonist and an ICS and in those already controlled in LABA/ICS combination therapy.	GREEN Included in the *Lincolnshire Joint Formulary.* *Licensed for children over 12 years.* *Sirdupla* MDI is the preferred product in adult patients,
Sodium hyaluronate 1% peri-articular injections (*SportVis* and *TendoVis*) (LSP Bio Ltd)	For the treatment of acute ankle sprain and epicondylalgia of the elbow (tennis elbow).	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*.

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the PACEF website (http://lincolnshire-pacef.nhs.uk); 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.**

RAPID DRUG ASSESSMENT: *SALMETEROL AND FLUTICASONE PROPIONATE 25MCG/125MCG AND 25MCG/250MCG METERED DOSE INHALER (SIRDUPLA)*

Sirdupla is a new generic salmeterol/fluticasone propionate combination metered dose inhaler (MDI) launched by Mylan as a lower cost alternative to *Seretide 125 and 250 Evohaler*.

Sirdupla is a combination MDI containing salmeterol and fluticasone propionate available in two different strengths: salmeterol 25mcg/fluticasone propionate 125mcg and 25mcg/250mcg. It holds a marketing authorisation for the regular treatment of asthma in adults where use of a long-acting β2 agonist (LABA) and inhaled corticosteroid (ICS) in combination is appropriate. It can be used in patients over 18 not adequately controlled with an 'as needed' inhaled short-acting β2 agonist and an ICS and in those already controlled on LABA/ICS combination therapy.

Pharmacodynamic and pharmacokinectic studies have demonstrated that *Sirdupla* is directly bioequivalent to the two comparable strengths of *Seretide Evohaler*, *Seretide 125* (salmeterol 25mcg/fluticasone propionate 125mcg) and *Seretide 250* (salmeterol 25mcg/fluticasone propionate 250 mcg). There is currently no *Sirdupla* equivalent to *Seretide 50 Evohaler* (salmeterol 25mcg/ fluticasone propionate 50mcg). The *Seretide 50* Evohaler is licensed for adults and children over 5 years; Seretide 125 Evohaler and Seretide 250 Evohaler are licensed for adults and children over 12 years. Sirdupla MDIs are only licensed for adult patients.

A cost comparison reveals that the *Sirdupla* MDIs are 25% lower in cost than equivalent *Seretide Evohalers.*

Drug	**Number of doses**	**Cost (£)**
Sirdupla 25/125 MDI (salmeterol 25 mcg/ fluticasone propionate 125 mcg per dose) (Mylan)	120	£26.25
Seretide 125 Evohaler (salmeterol 25mcg/ fluticasone propionate 125mcg per dose) (A&H)	120	£35.00
Sirdupla 25/250 MDI (salmeterol 25 mcg/ fluticasone propionate 250 mcg per dose) (Mylan)	120	£44.61

Seretide Evohaler 250 (salmeterol 25mcg/ fluticasone propionate 250mcg per dose) (A&H)	120	£59.48

Assuming a 100% switch from *Seretide 125* and *250 Evohalers* to equivalent strength *Sirdupla* MDIs, the potential QIPP savings available to the Lincolnshire CCGs are as follows:

	Potential saving
Lincolnshire East CCG	£154,726
Lincolnshire West CCG	£135,459
South Lincolnshire CCG	£126,752
South West Lincolnshire CCG	£101,621
Lincolnshire	£518,558

Based on the exclusions detailed above, specifically around the need to continue to prescribe Seretide 50,125 and 250 Evohalers for children, it must be stressed that these 100% savings figures are not fully achievable.

PACEF Recommendation:
Both *Sirdupla* 25/125 MDI and *Sirdupla* 25/250 MDI are designated GREEN and approved for use on the *Lincolnshire Joint Formulary*. Prescribers are urged to review all adult patients currently prescribed the *Seretide 125 Evohaler* or the *Seretide 250 Evohaler* with a view to switching patients to the equivalent strength *Sirdupla* MDI. In order to ensure that the NHS pays for the lower cost *Sirdupla* product rather than the NHS reimbursement price for an open generic prescription (based on the originator brand *Seretide Evohaler* price), prescribers are asked to ensure that *Sirdupla* is always prescribed by brand. All three strengths of the *Seretide Evohaler* (50, 125 and 250) remain available on the *Lincolnshire Joint Formulary* designation GREEN, primarily for use in children. *Sirdupla* 25/125 MDI and 25/250 MDI are only licensed for use in adult patients.

NEW DRUG ASSESSMENT: *BUDESONIDE 9MG SUSTAINED RELEASE GASTRO-RESISTANT TABLETS (CORTIMENT)*

A new budesonide 9mg sustained release tablet formulations is available (*Cortiment*), but local gastro-enterologists prefer 3mg preparations (*Budenofalk* and *Entocort CR*) for ease of titration and step-down.

There are a number of oral budesonide products with marketing authorisations for the treatment of various manifestations of inflammatory bowel disease. The table below summarizes licensed indications:

Product	**Marketing authorisation**
Budesonide 3mg gastro-resistant capsules (*Budenofalk*) (Dr Falk)	For the induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon. For the symptomatic relief of chronic diarrhoea due to collagenous colitis. For autoimmune hepatitis.
Budesonide 9mg gastro-resistant granules (*Budenofalk Granules*) (Dr Falk)	For the induction of remission in patients with mild to moderate active Crohn's disease affecting the ileum and/or the ascending colon. For the symptomatic relief of chronic diarrhoea due to collagenous colitis.
Budesonide 9mg sustained release gastro-resistant tablets (*Cortiment*) (Ferring)	For the induction of remission in mild to moderate active ulcerative colitis, where mesalazine is not sufficient.
Budesonide 3mg gastro-resistant sustained release capsules	For the induction of remission in patients with mild to moderate Crohn's disease affecting the ileum and/or the

(*Entocort CR*) (AstraZeneca)	ascending colon.

At present, budesonide 3mg gastro-resistant sustained release capsule (*Entocort CR*) is the only product listed on the *Lincolnshire Joint Formulary*; designated AMBER without shared care. Alternative corticosteroids on *Formulary* for the treatment of inflammatory bowel disorders are prednisolone tablets and rectal hydrocortisone and prednisolone formulations.

Budesonide 9mg sustained release gastro-resistant tablets (*Cortiment*) enable a single 9mg dose to be given daily rather than three 3mg capsules. *Cortiment* is also significantly lower in cost than *Entocort CR*, but more expensive than *Budenofalk* (see cost comparison):

Product	**Recommended dose**	**Cost (28 days)**
Budesonide 3mg gastro-resistant capsules (*Budenofalk*) (Dr Falk)	3mg three times daily for up to a maximum of 8 weeks or until remission in autoimmune hepatitis.	£63.04
Budesonide 9mg gastro-resistant granules (*Budenofalk Granules*) (Dr Falk)	9mg sachet once daily in the morning for a maximum of 8 weeks.	£63.00
Budesonide 9mg sustained release gastro-resistant tablets (*Cortiment*) (Ferring)	9mg once daily in the morning for a maximum of 8 weeks.	£70
Budesonide 3mg gastro-resistant sustained release capsules (*Entocort CR*) (AstraZeneca)	Three 3mg capsules once daily in the morning for up to 8 weeks.	£83.16

PACEF Recommendation:
Budesonide 3mg gastro-resistant capsules (*Budenofalk*) are designated AMBER without shared care and preferred first line for the induction of remission in patients with mild to moderate Crohn's disease as they are lower cost; they are also approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. Budesonide 3mg gastro-resistant sustained release capsules (*Entocort CR*) are designated AMBER without shared care and recommended second line for the same indication; they are already included in the *Lincolnshire Joint Formulary*. Advice from local gastroenterologists is that budesonide products available in the 3mg strength are preferred as this allows for dose adjustment and for doses to be gradually tailed off. In order to ensure continuation of supply it is recommended that these products are prescribed by brand. Budesonide 9mg gastro-resistant granules (*Budenofalk Granules*) and budesonide 9mg sustained release gastro-resistant tablets (*Cortiment*) are designated RED-RED and should not be prescribed.

RAPID COST COMPARISON: *COSMOCOL RANGE OF MACROGOL PRODUCTS*

The proliferation of new lower cost macrogol containing laxatives (*CosmoCol*, *Laxido Orange* and *Molaxole*) means that the originator brand *Movicol* no longer has a significant role.

A new lower cost range of macrogol containing osmotic laxatives indicated for the treatment of chronic constipation and the resolution of faecal impaction has been launched in the UK under the *CosmoCol* brand name. The products in the range include:

Product	Indications
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*CosmoCol*) (Stirling Anglian)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.
Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes powder for oral solution (*CosmoCol Half*) (Stirling Anglian)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.
Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes, powder for oral solution (*CosmoCol Paediatric*) (Stirling Anglian)	For the treatment of chronic constipation in children Aged from 2 to 11 years. For resolving faecal impaction in children aged 5 years and over.

Competing products are licensed as follows:

Product	Indications
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (Compound macrogol oral powder) (Galen)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Laxido Orange*) (Galen)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Molaxole*) (Meda)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Movicol*) (Norgine)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.
Macrogol (polyethylene glycol) 3350 6.563g plus electrolytes powder for oral solution (*Movicol-Half*) (Norgine)	For chronic constipation and faecal impaction in adults, the elderly and adolescents. Not recommended for children under 12 years.
Macrogol (polyethylene glycol) 3350 6.563g plus electrolytes, powder for oral solution (*Movicol Paediatric*) (Stirling Anglian)	For the treatment of chronic constipation in children Aged from 2 to 11 years. For children under 2 see *BNF for Children.* For resolving and prevention of faecal impaction in children aged 5 years and over. For children under 5 years see *BNF for Children*.

Macrogol containing laxatives are already approved for use on the *Lincolnshire Joint Formulary* with *Laxido Orange* and *Molaxole* designated as the preferred brands. A cost comparison of the *CosmoCol* range with alternative macrogol containing laxatives reveals that *CosmoCol* is also a lower cost brand (lower cost products are highlighted in bold):

Product	Flavour	Pack size	Cost (£)
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (Compound macrogol oral powder) (Galen)	Unflavoured	20 30	£4.45 £6.68
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*CosmoCol*) (Stirling Anglian)	**Orange, lemon and lime; Orange**	**20 30**	**£2.75 £3.95**
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*CosmoCol*) (Stirling Anglian)	**Lemon & lime**	**20 30**	**£3.56 £5.34**
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (CosmoCol) (Stirling Anglian)	**Unflavoured**	**30**	**£3.95**
Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes powder for oral solution (*CosmoCol Half*) (Stirling Anglian)	**Orange, lemon and lime**	**30**	**£2.99**
Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes powder for oral solution (*CosmoCol Paediatric*) (Stirling Anglian)	**Orange, lemon and lime**	**30**	**£2.99**
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Laxido Orange*) (Galen)	**Orange**	**20 30**	**£2.85 £4.27**
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Molaxole*) (Meda)	**Lemon**	**20 30**	**£3.78 £5.68**
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Movicol*) (Norgine)	Lime and lemon	20 30 50	£4.45 £6.68 £11.13
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Movicol*) (Norgine)	Chocolate	30	£6.68
Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Movicol*) (Norgine)	Unflavoured	30 50	£6.68 £11.13
Macrogol (polyethylene glycol) 3350 6.563g plus electrolytes powder for oral solution (*Movicol-Half*) (Norgine)	Lime and lemon	20 30	£2.92 £4.38
Macrogol (polyethylene glycol) 3350 6.563g plus electrolytes powder for oral solution (*Movicol Paediatric*) (Norgine)	Chocolate; Unflavoured	30	£4.38

Ref: *MIMS* June 2015

<u>PACEF Recommendation</u>:
There are now a number of macrogol containing laxatives available that are significantly lower cost than the originator brand, *Movicol*. Prescribers are advised to use a lower cost brand wherever a macrogol containing laxative is indicated. For adults, the elderly and adolescents the following products are designated GREEN and

approved for use on the Lincolnshire Joint Formulary: Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*CosmoCol*); Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes powder for oral solution (*CosmoCol Half*); Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Laxido Orange*); and Macrogol (polyethylene glycol) 3350 13.125g plus electrolytes powder for oral solution (*Molaxole*). For children, Macrogol (polyethylene glycol) 3350 6.9g plus electrolytes, powder for oral solution (*CosmoCol Paediatric*) (see product SPC for details). In order to ensure that the preferred product is supplied, these products should be prescribed by brand name. The *Movicol* range of products are higher cost in comparison to equivalent preparations and should no longer be prescribed. *Movicol*, *Movicol-Half* and *Movicol Paediatric* are designated RED-RED and have been removed from the *Lincolnshire Joint Formulary*.

RAPID DRUG ASSESSMENT: *SODIUM HYALURONATE 1% 1.2ML PRE-FILLED SYRINGE (TENDOVIS AND SPORTVIS)*

***BNF* advice precludes the prescribing of hyaluronic acid and its derivatives for joint inflammation.**

SportVis and *TendoVis* are new sodium hyaluronate 1% peri-articular injections licensed for the treatment of acute ankle sprain and epicondylalgia of the elbow (tennis elbow). Standard *BNF* advice is that hyaluronic acid and its derivatives are not recommended for joint inflammation.

PACEF Recommendation:
Sodium hyaluronate 1% 1.2ml peri-articular injection pre-filled syringe (SportVis and TendoVis) are not recommended for use and are designated RED-RED. They have not been approved for inclusion in the *Lincolnshire Joint Formulary*.

RAPID DRUG ASSESSMENT: *LECICARBON C FOR CONSTIPATION, BOWEL CLEARANCE AND DIAGNOSTIC PROCEDURES IN CHILDREN UNDER 12*

A new suppository formulation for the treatment of constipation in children is not approved for use.

Lecicarbon C suppositories contain sodium hydrogen carbonate 250mg and sodium dihydrogen phosphate 340mg per suppository. They hold a marketing authorisation for constipation, bowel clearance and diagnostic procedures in children under 12.

Carbon dioxide is the main constituent of the gaseous products of metabolism which are formed on digestion of the intestinal contents. Of all the intestinal gases, it is the one which causes the most intense stimulation of movement of the rectum. When the *Lecicarbon C* suppository comes into contact with moisture in the intestine, carbon dioxide is liberated causing the physical induction of reflex bowel evacuation. The evacuation process occurs within 15 to 30 minutes of inserting the suppository without causing irritation, cramps or other side effects.

The product has been available in Germany for many years and has been approved for use within other member states of the European Union based on the Mutual Recognition Procedure.

Lecicarbon C suppositories are relatively expensive in comparison with alternatives: 10 suppositories cost £8.20.

PACEF Recommendation:
In view of the lack of comparative data against alternatives and the relatively high cost of the product, *Lecicarbon C* suppositories are designated RED-RED and have not been approved for inclusion in the *Lincolnshire Joint Formulary.*

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

SGLT2 INHIBITORS (CANAGLIFLOZIN , DAPAGLIFLOZIN, EMPAGLIFLOZIN): RISK OF DIABETIC KETOACIDOSIS

Sodium glucose co-transporter 2 (SGLT2) inhibitors are licensed for use in adults with type 2 diabetes to improve glycaemic control. There are now three drugs in this class with a UK marketing authorisation; canagliflozin, dapagliflozin and empagliflozin. The available formulations are as follows:

Dapagliflozin tablets (5 mg and 10 mg) - *Forxiga*▼
Dapagliflozin/metformin tablets (5 mg/850 mg and 5 mg/1000 mg) *Xigduo*▼
Canagliflozin tablets (100 mg and 300 mg) *Invokana*▼
Canagliflozin/metformin tablets (50 mg/850 mg, 50 mg/1000 mg, 150mg/850mg, *Vokanamet*▼150mg/1000mg)
Empagliflozin tablets (10 mg and 25 mg) *Jardiance*▼

Reports of diabetic acidosis

Serious and life-threatening cases of diabetic ketoacidosis (DKA) have been reported in patients taking SGLT2 inhibitors. In several cases, blood glucose levels were only moderately elevated (e.g. <14 mmol/L or 250 mg/dL), which is **atypical for DKA.** This atypical presentation could delay diagnosis and treatment. As a result of this, it is important to inform patients on SGLT2 inhibitors of the warning signs and symptoms of DKA (e.g. nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness) and test for raised ketones in patients with these signs and symptoms.

Half of the reported cases occurred during the first 2 months of treatment. Some cases occurred shortly after stopping the SGLT2 inhibitor. One third of the cases involved off-label use in patients with type 1 diabetes; prescribers are reminded that this drug class is **not licensed** for the treatment of type 1 diabetes.

The underlying mechanism for SGLT2 inhibitor-associated DKA has not been established. EU medicines regulators are investigating this concern and will report back at a later date.

In response to rising concerns, the MHRA have issued the following advice. When treating patients who are taking an SGLT2 inhibitor (canagliflozin, dapagliflozin or empagliflozin):

- test for raised ketones in patients with symptoms of diabetic ketoacidosis (DKA); omitting this test could delay diagnosis of DKA.
- if you suspect DKA, stop SGLT2 inhibitor treatment.
- if DKA is confirmed, take appropriate measures to correct the DKA and to monitor glucose levels.
- inform patients of the symptoms and signs of DKA; advise them to get immediate medical help if these occur.
- be aware that SGLT2 inhibitors are not approved for treatment of type 1 diabetes.

- please continue to report suspected side effects to SGLT2 inhibitors or any other medicines on a Yellow Card.

PACEF Comment
All three SGLT2 inhibitors have been recommended by NICE for the treatment of type 2 diabetes and are included on the *Lincolnshire Joint Formulary* for use within licensed indications and NICE treatment criteria. For the most recent PACEF advice, see *PACE Bulletin* Volume 9 Number 9 (June 2015).

HIGH-DOSE IBUPROFEN (≥2400MG/DAY): SMALL INCREASE IN CARDIOVASCULAR RISK

High-dose ibuprofen and cardiovascular risk

The MHRA and other EU medicines regulators have reviewed the safety of high-dose ibuprofen, following the publication of a meta-analysis of clinical trial data. This meta-analysis showed that people taking ≥2400 mg of ibuprofen per day are at a higher risk of arterial thrombotic events (heart attack, stroke) than people taking placebo. The review confirmed that this higher risk is similar to that seen with COX-2 inhibitors and diclofenac. No increased risk of arterial thrombotic events is seen with ibuprofen at doses up to 1200 mg per day (the highest dose available over the counter) compared with not taking ibuprofen. There are limited data on the risk with ibuprofen at doses between 1200 mg and 2400 mg per day. It is uncertain whether such doses are associated with an increased cardiovascular risk compared with not taking ibuprofen.

Possible interaction between ibuprofen and low-dose aspirin

The European review also considered the latest data on the possible interaction between ibuprofen and low-dose aspirin. The latest experimental data confirm previous findings that ibuprofen competitively inhibits the effect of low-dose aspirin on platelet aggregation in vivo, ex vivo and in vitro. It is uncertain if these data can be extrapolated to the clinical situation, and clinical data do not support a clinically meaningful interaction. However, the possibility that long-term, daily use of ibuprofen might reduce the cardio-protective effects of low-dose aspirin cannot be excluded. Occasional ibuprofen use is unlikely to have a clinically meaningful effect on the benefits of low-dose aspirin.

When prescribing an NSAID, prescribers are reminded:

- to base the decision to prescribe an NSAID on an assessment of the patient's individual risk factors, including any history of cardiovascular and gastrointestinal illness.
- that naproxen and low-dose ibuprofen (≤1200 mg per day) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs.
- to use the lowest effective dose for the shortest duration necessary to control symptoms and re-evaluate the patient's need for symptomatic relief and response to treatment periodically.
- to consider that no increase in cardiovascular risk is seen with ibuprofen at doses up to 1200 mg per day (the highest dose available over the counter) compared with not taking ibuprofen.

The MHRA have advised when prescribing or dispensing ibuprofen:

- to avoid use of high-dose ibuprofen (≥2400 mg per day) in patients with established:
    - ischaemic heart disease
    - peripheral arterial disease
    - cerebrovascular disease

    - congestive heart failure (New York Heart Association [NYHA] classification II-III)
    - uncontrolled hypertension
- to review the treatment of patients with the above conditions who are taking high-dose ibuprofen at their next routine appointment
- to carefully consider the benefits and risks before starting long-term ibuprofen treatment for patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking), particularly if high doses are required
- to remember that ibuprofen is contraindicated in patients with severe heart failure
- these recommendations also apply to dexibuprofen.

PACEF Comment:
In 2013, less than 1% of all prescriptions for ibuprofen in primary care in the UK were for 2400 mg per day or more. Our analysis of current ibuprofen prescribing data in Lincolnshire suggests that there are very few patients in county taking such high doses of ibuprofen. Prescribers are urged to review these patients in accordance with MHRA criteria.

INTRAUTERINE CONTRACEPTION: *UTERINE PERFORATION—UPDATED INFORMATION ON RISK FACTORS*

Intrauterine contraception includes levonorgestrel-releasing intra-uterine systems (IUSs) and copper intra-uterine devices (IUDs). IUSs are licensed for several gynaecological conditions including:

- long-term contraception (*Jaydess*, *Levosert*, *Mirena*)
- heavy menstrual bleeding (*Levosert*, *Mirena*)
- protection from endometrial hyperplasia during oestrogen replacement therapy (*Mirena*)

Use of intrauterine contraception can rarely result in uterine perforation. Perforation most often occurs during insertion, but might not be detected until some time later. The MHRA have received 114 Yellow Card reports of uterine perforation and 22 reports of devices becoming embedded in the uterus, cervix or other local tissues in association with use of levonorgestrel-releasing IUSs up to 12 February 2015.

EURAS-IUD study

The European Active Surveillance Study for Intrauterine Devices (EURAS-IUD) was an observational study which examined the risk of uterine perforation with intrauterine contraception. The study followed 43,078 women who used levonorgestrel-releasing IUSs and 18,370 women who used copper IUDs.

The risk of perforation was increased in the following instances:

- in women who were lactating (compared with women not lactating) at the time of insertion
- when the IUS or IUD was inserted up to 36 weeks (compared with more than 36 weeks) after giving birth

These risk factors were independent of the type of intrauterine contraception inserted.

The benefits of intrauterine contraception still strongly outweigh the rare risk of perforation for most women, including those who are lactating or have recently given birth. Therefore the MHRA have not put in place any new restrictions on use of intrauterine contraception based

on the study findings. The summaries of product characteristics and patient information leaflets have been updated with the relevant information.

The most important risk factors for uterine perforation are insertion during lactation and insertion in the 36 weeks after giving birth. Before inserting an IUS or IUD, women should be informed of the risk and the symptoms of perforation.

The MHRA advise that, before inserting an intrauterine system (IUS) or intrauterine device (IUD), the woman should be informed that perforation occurs in less than 1 in 1,000 women and that the symptoms include:

- severe pelvic pain after insertion (worse than period cramps).
- pain or heavy bleeding after insertion which continues for more than a few weeks.
- sudden changes in periods.
- pain during sex.
- not being able to feel the threads.

Women should be taught how to check their threads and told to return for a check-up if they cannot feel them (especially if they also have significant pain). Partial perforation may have occurred even if the threads can still be seen; consider this if there is severe pain following insertion.

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