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 21 **December 2015**

Merry Christmas and Happy New Year to all our readers

What's new this month?

- **Escalating prices of AMCo generic medicines have necessitated a review of prescribing guidance around a range of high-cost products including dipipanone 10mg/cyclizine 30mg tablets, fusidic acid 1% modified release eye drops, liothyronine 20 microgram tablets, phenindione 10mg and 25mg tablets and prednisolone 5mg soluble tablets (see page 3).**
- **Biosimilar insulin glargine 100 units per ml (*Abasaglar*) is now available and approved for use through the *Lincolnshire Joint Formulary*, designation GREEN; it is 15% lower in cost than *Lantus,* the originator brand, and should be preferred in new patients requiring insulin glargine (see page 6).**
- **Insulin glargine 300iu/ml (*Toujeo*) is approved for use through the *Lincolnshire Joint Formulary*, designation GREEN. It should only be initiated on the advice of a diabetologist or GPSI and reserved for those experiencing an unacceptable frequency and/or severity of nocturnal hypoglycaemia or attempting to achieve better hypoglycaemia control during treatment with established insulins (see page 9).**
- **NICE have just published an update to their clinical guideline on the management of type 2 diabetes and have updated their guidance on the role of insulin analogues (see page 9).**
- **Empagliflozin/metformin tablets (*Synjardy*) are designated GREEN and approved for use through the *Lincolnshire Joint Formulary* where a SGLT2 inhibitor is indicated in combination with metformin (see page 10).**
- **A new lower cost licensed formulation of midodrine 2.5mg and 5mg tablets (*Bramox*) is now available and preferred over unlicensed alternatives for the treatment of severe orthostatic hypotension; designation AMBER with shared care. Changes to the NHS reimbursement price mean that Lincolnshire CCGs can expect fortuitous savings of over £34,000pa. The shared care guideline is under review and will be updated and re-published next month. Generic prescribing is recommended (see page 11).**
- **Tafluprost 15mcg/timolol 5mg per ml preservative-free single use eye drops *(Taptiqom)* are designated AMBER without shared care and are preferred where a prostaglandin analogue/ beta-blocker preservative-free eye preparation is indicated in the treatment of ocular hypertension or open-angle glaucoma (see page 12).**
- **Lithium carbonate 250mg tablets previously known as *Camcolit* have been renamed as lithium carbonate Essential Pharma 250mg tablets; the strength and formulation remain the same. The higher strength lithium carbonate 400mg *Camcolit* prolonged release tablet has not been rebranded (see page 13).**

- **Review of prescribing data reveals that many prescriptions for lithium preparations are still prescribed generically despite a specific BNF caution around wide variation in bioavailability between preparations. Clinicians are urged to ensure that all lithium prescribing is brand specific. Clinicians are also reminded of the monitoring requirements for all patients taking lithium. Once the patient is stabilised, routine serum lithium monitoring should be done every three months with additional monitoring introduced if the patient develops significant intercurrent disease or there is a significant change in sodium level or fluid intake. Renal function, cardiac function and thyroid function should be monitored every 6 months (see page 13).**
- **Bayer have reduced the price of rivaroxaban (*Xarelto*) and discontinued the *Xarelto Rebate Scheme* from 1st December 2015. Fortuitous savings resulting from the price reduction across the Lincolnshire CCGs are likely to be in excess of £150,000pa (see page 13).**
- **This month sees the launch of a patient information leaflet on the subject of *Medicines and Your Kidneys* launched by the East Midlands Cardiovascular Strategic Clinical Network. Copies of the leaflet and supporting resources are in the process of being distributed to practices. Patients who should receive a copy of the leaflet include those on ACE inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs and metformin (see page 14).**

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SUMMARY OF PACEF DECISIONS: *OCTOBER 2015 UPDATE*

Drug	Indication(s)	Traffic Light and *Joint Formulary* Status
Dipipanone 10mg/cyclizine 30mg tablets (previously *Diconal*)	For moderate to severe pain	RED-RED The Controlled Drug Accountable Officer and Lincolnshire Police have requested that all prescribing should cease to mitigate the risk of drug misuse and diversion. Oral morphine or even oral oxycodone (for those intolerant of morphine) are preferred.
Empagliflozin/metformin tablets 5mg/ 850mg, 5mg/1000mg, 12.5mg/850mg and 12.5mg/1000mg (*Synjardy*) (Boehringer Ingelheim)	For the treatment of type 2 diabetes	GREEN Approved for inclusion in the Lincolnshire Joint Formulary.
Insulin glargine 100 units/ml injection (*Abasaglar*) cartridges and *KwikPen* (Eli Lilly and Company Ltd)	Treatment of diabetes mellitis in adults, adolescents and children aged 2 years and above.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary*
Insulin glargine 300units/ml injection (*Toujeo*) (Sanofi)	Treatment of diabetes mellitus in adults.	AMBER without shared care Approved for inclusion in the *Lincolnshire Joint Formulary*. Should only be initiated on the

		advice of a diabetologist or a GP with a specialist interest in diabetes for those experiencing an unacceptable frequency and/or severity of nocturnal hypoglycaemia or attempting to achieve better hypoglycaemia control during treatment with established insulins.
Levothyroxine sodium 25, 50 and 100 microgram tablets	Hypothyroidism	GREEN Included in the *Lincolnshire Joint Formulary*.
Liothyronine 20microgram tablets	Hypothyroidism	AMBER without shared care. For specialist initiation only. Included in the *Lincolnshire Joint Formulary.*
Lithium carbonate Essential Pharma 250mg tablet (Essential Pharma Ltd)	Treatment and prophylaxis of mania, bipolar disorder, recurrent depression, aggressive or self-harming behaviour	AMBER Included in the *Lincolnshire Joint Formulary.*
Midodrine hydrochloride 2.5mg and 5mg tablets *(Bramox)* (Brancaster Pharma)	For the treatment of severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate.	AMBER with shared care Included in the *Lincolnshire Joint Formulary* for this indication.
Tafluprost 15mcg/timolol 5mg per ml preservative-free single use eye drops *(Taptiqom)* (Santen)	For the treatment of ocular hypertension or open-angle glaucoma insufficiently responsive to beta-blockers (BBs) or prostaglandin analogues (PGA) alone.	AMBER without shared care. Approved for inclusion in the *Lincolnshire Joint Formulary*. Preferred where a PGA/BB preservative-free preparation is indicated.

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@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.**

REVIEW OF PRESCRIBING GUIDANCE IN RESPONSE TO AMCO PRICE INCREASES

Escalating prices of AMCo generic medicines have necessitated a review of prescribing guidance around a range of high-cost products including fusidic acid 1% modified release eye drops, liothyronine 20 microgram tablets, phenindione 10mg and 25mg tablets and prednisolone 5mg soluble tablets.

Amdipharm Mercury Company Limited (AMCo) market a number of generic medicines that are in Category C of the *Drug Tariff*. All of these medicines have been available for many years and the majority were historically very inexpensive, mostly available as lower cost brands. Since around 2012 (although this varies between products) many of these low cost brands have been discontinued and re-launched as generics, by the same company, usually at a much higher price than the originator brand.

The table below illustrates some of the most significant price increases in the last year:

Product	**Quantity**	**Previous Price (November 2014 *Drug Tariff*)**	**Current Price (November 2015 *Drug Tariff*)**
Demeclocycline 150mg capsules	28	£81.49	£160.89
Dipipanone 10mg/cyclizine 30mg tablets (previously *Diconal*)	50	£129.74	£353.06
Flumetasone 0.02%/clioquinol 1% ear drops (*Locorten-Vioform*)	7.5ml	£1.76	£10.37
Flumetasone 0.02%/clioquinol 1% ear drops (*Locorten-Vioform*)	10ml	£2.35	£13.82
Fusidic acid 1% modified release eye drops (previously *Fucithalmic*)	5g	£7.57	£29.06
Gentamicin 0.3%/Hydrocortisone acetate 1% ear drops (previously *Gentisone HC*)	10ml	£4.76	£23.92
Liothyronine 20microgram tablets	28	£102.30	£198.62
Phenindione 10mg tablets	28	£79.01	£519.98
Phenindione 25mg tablets	28	£99.89	£519.98
Phenoxybenzamine 10mg capsules	30	£32.87	£97.38
Prednisolone 5mg soluble tablets	30	£42.78	£53.48
Sulfinpyrazone 100mg tablets	84	£41.25	£102.96
Sulfinpyrazone 200mg tablets	84	£79.00	£147.65
Triamterene 50mg capsules	30	£19.95	£41.90
Trifluoperazine 1mg tablets	112	£54.00	£54.00
Trifluoperazine 5mg tablets	112	£77.00	£123.20

The prices of many AMCo generics have been steadily increasing since 2010. The scale of these price increases is illustrated below:

Drug	**Jan 2010 MIMS**	**AMCo Nov 2015**	**% increase since 2010**
Liothyronine 20mcg tablets (28 tablets)	£23.77	£198.62	736%
Dipipanone 10mg/cyclizine 30mg tablets (previously *Diconal*) (50 tablets)	£9.97	£353.06	3,441%
Demeclocycline 150mg	£16.02	£160.89	904%

capsules (28 capsules)			
Indoramin 25mg tablets (84 tablets)	£9.00	£60.26	569%
Phenindione 10mg tablets (28 tablets)	£18.34	£519.98	2735%
Prednisolone 5mg soluble tablets (30 tablets)	£7.45	£53.48	618%

PACEF Recommendations:

(1) Demeclocycline remains on the *Lincolnshire Joint Formulary* solely for the treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone. It is not recommended for any other indication.

(2) In May 2011 at the request of the Controlled Drug Accountable Officer and Lincolnshire Police, PACEF issued guidance urging prescribers to review all patients remaining on dipipanone 10mg/cyclizine 30mg tablets (or *Diconal*) with a view to changing to alternative therapy. This request was made due to the potential for drug misuse and diversion. Since December Quarter 2010, prescribing has declined from 300 prescriptions per quarter to 96 (costing £32,644, an average of £340 per prescription). Dipipanone 10mg/cyclizine 30mg tablets are designated RED-RED and should no longer be prescribed. The opioid of choice for moderate to severe pain is oral morphine. For those patients intolerant of morphine, oxycodone can be considered as an alternative. It is illegal to prescribe dipipanone for addiction unless the GP holds a license (see *PACE Bulletin* Vol 5 No 8 (May 2011)).

(3) With flumetasone 0.02%/clioquinol 1% ear drops (previously *Locorten-Vioform*) and gentamicin 0.3%/hydrocortisone acetate 1% ear drops (previously *Gentisone HC*) becoming increasingly expensive, lower cost *Formulary* approved alternatives such as *Sofradex* ear drops (dexamethasone 0.05%/framycetin sulfate 0.5%/gramicidin 0.005%) or *Betnesol N* ear drops (betamethasone 0.1%/neomycin 0.5%) should be preferred for eczematous inflammation in otitis externa.

	Pack size	Cost
Betamethasone 0.1%/neomycin 0.5% ear drops (*Betnesol N*)	10ml	£2.32
Dexamethasone 0.05%/framycetin sulfate 0.5%/gramicidin 0.005% ear drops (*Sofradex*)	10ml	£6.25
Flumetasone 0.02%/clioquinol 1% ear drops (*Locorten-Vioform*)	7.5ml	£10.37
Flumetasone 0.02%/clioquinol 1% ear drops (*Locorten-Vioform*)	10ml	£13.82
Gentamicin 0.3%/Hydrocortisone acetate 1% ear drops (previously *Gentisone HC*)	10ml	£23.92

(4) Problems around the escalating price of fusidic acid 1% modified release eye drops (previously *Fucithalmic*) were raised in *PACE Bulletin* Volume 9 No 18 (November 2015). Standard advice is to ensure that chloramphenicol 0.5% eye drops are preferred first line where antibiotic treatment of conjunctivitis is indicated.

(5) All patients prescribed liothyronine sodium 20microgram tablets for hypothyroidism should be reviewed to ensure that levothyroxine is not an appropriate alternative therapy. Levothyroxine is now significantly lower cost than liothyronine (see cost comparison below). Liothyronine sodium 20

microgram tablets are designated AMBER without shared care and should only be prescribed following specialist initiation.

	Cost (28 tablets)
Levothyroxine sodium 25 microgram tablets	£3.11
Levothyroxine sodium 50 microgram tablets	£2.11
Levothyroxine sodium 100 microgram tablets	£2.12
Liothyronine 20microgram tablets	£198.62

(6) All patients prescribed phenindione 10mg and 25mg tablets should be reviewed and, where possible, transferred to lower cost anticoagulation. It must be stressed that even newer oral anticoagulants are significantly lower cost than phenindione at present. NOAC SPCs and PACEF guidance provide details on how to transfer from vitamin K antagonists to the preferred NOAC.

	Dose	**Cost (28 days)**
Phenindione 25mg tablets	**50 to 150mg daily**	**£1,039.96 to £3,119.88**
Apixaban 2.5mg tablets (*Eliquis*) (Bristol-Myers Squibb Pharmaceuticals Ltd)	2.5mg twice daily	£61.50
Apixaban 5mg tablets (*Eliquis*) (Bristol-Myers Squibb Pharmaceuticals Ltd)	5mg twice daily	£61.50
Dabigatran 150mg capsules (*Pradaxa)* (Boehringer Ingelheim Ltd)	150mg twice daily	£61.51
Dabigatran 110mg capsules (*Pradaxa*) (Boehringer Ingelheim Ltd)	110mg twice daily	£61.51
Edoxaban 30mg tablets (*Lixiana*) (Daiichi Sankyo)	30mg once daily	£58.80
Edoxaban 60mg tablets (*Lixiana*) (Daiichi Sankyo)	60mg once daily	£58.80
Rivaroxaban 20mg tablets (*Xarelto*) (Bayer plc)	20mg once daily	£50.40

(7) Existing PACEF advice published in July 2015, advises prescribers to review all patients currently prescribed prednisolone soluble tablets 5mg. Both prednisolone 1mg and 5mg tablets are relatively small and do not present swallowing difficulties for most patients. Additionally, prednisolone 1mg and 5mg tablets can be dispersed in water to make a fine suspension (unlicensed use). The potential saving in Lincolnshire if only half of existing prescriptions for prednisolone soluble tablets 5mg were changed to standard prednisolone tablets is over £120,000pa (see *PACE Bulletin* Vol 9 No 11 (July 2015)).

NEW PRODUCT ASSESSMENT: *BIOSIMILAR INSULIN GLARGINE 100 UNITS/ML INJECTION (ABASAGLAR)*

Biosimilar insulin glargine 100 units per ml (*Abasaglar*) is now available and approved for use through the Lincolnshire Joint Formulary, designation GREEN; it is 15% lower in cost than *Lantus,* the originator brand, and should be preferred in new patients requiring insulin glargine

Abasaglar is a new biosimilar form of insulin glargine 100 units/ml recently launched by Lilly. It holds an identical marketing authorisation to the originator product, *Lantus.* This is the first of the biosimilar insulins to reach the UK marketplace with more expected within the next two years*. Abasaglar* is available in the pre-filled *Kwikpen* and as 3ml cartridges to be used in

Lilly insulin compatible devices such as the re-usable *Savvio* pen and the *AutoPen Classic* and *HumaPen* ranges.

NICE have issued generic advice on the use of biosimilars stating that where their guidance exists on an originator product this also applies to licensed comparable biosimilar products that subsequently appear on the market. This means that NICE guidance on the role of insulin analogues, recently updated in clinical guidelines on the treatment of both type 1 and type 2 diabetes, also applies to *Abasaglar*. PACEF guidance on the role of insulin analogues also applies with an update due to be published in January 2016.

In order to assess the product, PACEF examined a number of peer reviews that had already been published. The Midlands Therapeutics Review and Advisory Committee (MTRAC) acknowledge the safety and efficacy of the product in comparison to the originator brand, *Lantus*, and have advised that *Abasaglar* should be considered for use in new patients and in patients assessed to be in need of a change in medication. They have not recommended therapeutic switching from *Lantus* to *Abasaglar* despite the significantly lower price (15% lower) until clinical experience with the treatment and the delivery device has been gained.

Trent Medicines Information Service has also issued a briefing on the introduction of *Abasaglar.* It advises that the two insulin glargine 100units/ml products are not directly interchangeable and takes a similar view to MTRAC in advising that *Abasaglar* should be restricted to new patients and to those under review due to suboptimal control of their condition.

UK Medicines Information has also issued a product safety assessment of both of the new insulin glargines, *Abasaglar* and *Toujeo* (see below). The report warns of a risk of confusion between the three different brands now available and makes recommendations on how to reduce this risk. Prescribers are advised to ensure that all insulin glargine is now prescribed by brand. When storing the different products in dispensary refrigerators care should be taken to ensure that each product is clearly differentiated on the shelf and that each dispensed prescription is carefully checked to ensure that the right product at the right dose has been dispensed. Care should also be taken to ensure that the correct compatible device is being used for each product. Switching between brands should only occur as part of a managed switch programme; PACEF will evaluate the prospect of product switching in the new year once experience with the *Abasaglar* product and associated devices has been gained.

A cost comparison between *Abasaglar* and *Lantus* reveals the following:

Drug	**Pack size**	**Cost**
Insulin glargine 100 units/ml injection (*Abasaglar*) (Eli Lilly and Company Ltd)	5 x 3ml *KwikPen*	£35.28 £35.28
Insulin glargine 100 units/ml injection (*Abasaglar*) (Eli Lilly and Company Ltd)	5 x 3ml cartridges for *Autopen Classic* or *HumaPen* ranges	£35.28
Insulin glargine 100 units/ml injection (*Lantus*) (Sanofi)	5 x 3ml *SoloStar* pre-filled pen	£41.50
Insulin glargine 100 units/ml injection (*Lantus*) (Sanofi)	5 x 3ml cartridges for *Autopen 24* and *ClikSTAR* device	£41.50
Insulin glargine 100 units/ml injection (*Lantus*) (Sanofi)	10 ml vial	£30.68
Insulin glargine 300units/ml injection (*Toujeo*) (Sanofi)	3 x 1.5ml *SoloStar* pre-filled pen	£33.13

MTRAC have estimated that a 40 unit daily dose of insulin glargine *Lantus* would cost £404 per patient per year; the same dose of *Abasaglar* would cost £343 per patient per year.

Lincolnshire prescribing preference for medium to long-acting insulin analogues as opposed to standard NPH insulins is particularly high as illustrated in the table below with insulin glargine (*Lantus*) being a strong contributor to this profile:

Percentage of intermediate and long-acting insulins prescribed as insulin analogues (insulin glargine or insulin determir) (Items)	**September 2014 Quarter**	**September 2015 Quarter**
Lincolnshire East CCG	90.7%	91.71%
Lincolnshire West CCG	89.2%	90.26%
South Lincolnshire CCG	90.71%	90.93%
South West Lincolnshire CCG	88.36%	90.07%
Lincolnshire	89.93%	90.93%
National	80.3%	78.88%

In general, Lincolnshire CCGs are 11% higher than national average against this indicator, suggesting that insulin analogues are used more readily in county than elsewhere. Trends in the last year have seen all four Lincolnshire CCGs increase their proportional use of insulin analogues while nationally proportional use has been in decline.

The potential annual cost saving in Lincolnshire if all insulin glargine prefilled pens and 3ml cartridges were switched to *Abasaglar* is £231,000 broken down to CCG level as follows:

CCG	Annual saving
LECCG	£89,180
LWCCG	£57,660
SLCCG	£45,780
SWLCCG	£38,324

PACEF Recommendation

Insulin glargine 100 units/ml injection (*Abasaglar*) is designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*. It should be initiated as the insulin glargine of choice in new patients and be considered as a lower cost alternative to *Lantus* in those under review due to suboptimal control of their condition. Switching between brands should only occur as part of a managed switch programme; PACEF intend to evaluate the prospect of product switching in the new year once experience with the *Abasaglar* product and associated devices has been gained. Our intention is to work with diabetic specialists in both ULH and Lincolnshire Community Health Services to agree on a shared approach to the introduction of biosimilar insulins in 2016 and beyond. There are now three different brands of insulin glargine available and the risk of confusion in terms of product, strength and dose is high. Prescribers are advised to ensure that all insulin glargine is now prescribed by brand to minimise the risk of dispensing error. In addition, when storing the different products in dispensary refrigerators care should be taken to ensure that each product is clearly differentiated on the shelf and that each dispensed prescription is carefully checked. Care should also be taken to ensure that the compatible delivery device is being used for each product. For updated NICE guidance on the prescribing of insulin analogues in type 2 diabetes mellitus see below.

NEW PRODUCT ASSESSMENT: *INSULIN GLARGINE 300IU/ML (TOUJEO)*

Insulin glargine 300iu/ml (*Toujeo*) is approved for use through the *Lincolnshire Joint Formulary*, designation GREEN. It should only be initiated on the advice of a diabetologist or GPSI and reserved for those experiencing an unacceptable frequency and/or severity of nocturnal hypoglycaemia or attempting to achieve better hypoglycaemia control during treatment with established insulins.

Insulin glargine 300iu/ml (*Toujeo*) is a new higher strength insulin glargine formulation available in a pre-filled pen with a maximum dial dose of 80iu. It is claimed to form a more compact subcutaneous depot on administration which allows for more prolonged release over a 24 hour period. PACEF reviewed a series of four clinical trials known as the EDITION studies. The primary outcome of the trials confirmed that insulin glargine 300iu/ml is non-inferior in terms of efficacy to the established 100iu/ml preparation. Secondary outcome data suggests that the 300iu/ml preparation may be superior to 100iu/ml in terms of reduced rates of nocturnal hypoglycaemia due to a slower more prolonged release, although the EDITION studies were not powered to prove this. The Scottish Medicines Consortium have recently approved insulin glargine 300iu/ml (*Toujeo*) for use in NHS Scotland 'for those at risk of experiencing unacceptable frequency and/or severity of nocturnal hypoglycaemia or attempting to achieve better hypoglycaemia control during treatment with established insulins'. A NICE Evidence Summary of New Medicines review states that *Toujeo* offers no benefit over *Lantus* in terms of reduced hypoglycaemic events on the basis that the EDITION studies do not demonstrate statistical significance around the secondary outcome.

PACEF Recommendation:
Insulin glargine 300iu/ml (*Toujeo*) is designated AMBER without shared care and should only be initiated on the advice of a diabetologist or a GP with a specialist interest in diabetes. It is approved for inclusion in the *Lincolnshire Joint Formulary* for those experiencing an unacceptable frequency and/or severity of nocturnal hypoglycaemia or attempting to achieve better hypoglycaemia control during treatment with established insulins. For updated NICE guidance on the prescribing of insulin analogues in type 2 diabetes mellitus see below.

NICE GUIDELINE NG28: *TYPE 2 DIABETES IN ADULTS – MANAGEMENT* (DECEMBER 2015)

Updated guidance on the prescribing of insulin-based treatments in patients with type 2 diabetes

NICE have just published an update to their clinical guideline on the management of type 2 diabetes and have updated their guidance on the role of insulin analogues as follows. Prescribers are reminded that insulin analogues such as glargine and determir are only considered first line within particular criteria as defined below:

- Offer NPH insulin injected once or twice daily according to need.
- Consider starting both NPH and short-acting insulin (particularly if the person's HbA1c is 75mmol/mol (9.0%) or higher, administered either separately or as a pre-mixed (biphasic) human insulin preparation.
- **Consider using insulin determir or insulin glargine as an alternative to NPH if: (1) the person needs assistance from a carer or healthcare professional to inject insulin (determir or glargine would reduce frequency of injections from**

twice to once daily); (2) the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes; or (3) the person would otherwise need twice daily NPH insulin in combination with oral glucose lowering drugs.

- Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations if: (1) a person prefers injecting insulin immediately before a meal; or (2) hypoglycaemia is a problem; or (3) blood glucose levels rise markedly after meals.
- **Consider switching to insulin determir or insulin glargine from NPH insulin in type 2 diabetics who (1) do not reach their target HbA1c because of significant hypoglycaemia or (2) who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached; or (3) who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to the long-acting insulin analogues was made; or (4) who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections.**
- Monitor people on a basal insulin regime (NPH insulin, insulin determir, insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed biphasic insulin preparation).
- Monitor people on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin determir or insulin glargine, if blood glucose control remains inadequate.

A more detailed review of the updated NICE clinical guideline on the management of type 2 diabetes will form the basis of a *PACE Bulletin* special early in the new year.

NEW PRODUCT ASSESSMENT: *EMPAGLIFLOZIN/METFORMIN TABLETS (SYNJARDY)*

Empagliflozin/metformin tablets (*Synjardy*) are designated GREEN and approved for use through the *Lincolnshire Joint Formulary* where a SGLT2 inhibitor is indicated in combination with metformin.

Empagliflozin (*Jardiance*) is a sodium-glucose co-transporter 2 (SGLT2) inhibitor licensed for the treatment of type 2 diabetes as monotherapy and in combination with insulin and other antidiabetic drugs. It has been approved by NICE for use as part of dual therapy, triple therapy or in combination with insulin in the treatment of type 2 diabetes. PACEF has evaluated all three SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) and has approved them all for inclusion in the *Lincolnshire Joint Formulary* in line with NICE guidance, designation GREEN.

All three of the SGLT2 inhibitors are marketed alone and as combination products with metformin. The most recently launched of these products is an empagliflozin and metformin combination product known as *Synjardy*. A cost comparison of *Synjardy* with other comparable SGLT2 inhibitor/metformin combination products appears below and reveals that all of the products are identically priced and that all of them are no more expensive in combination with metformin than as single component therapies (i.e. the metformin is provided at no extra cost).

Drug	Daily dose	Cost (£) Pack size	Cost 28 days
Empagliflozin/metformin tablets 5mg/ 850mg (*Synjardy*) (Boehringer Ingelheim)	1 twice daily	£36.59 (28)	£36.59
Empagliflozin/metformin tablets 5mg/1000mg (*Synjardy*) (Boehringer Ingelheim)	1 twice daily	£36.59 (28)	£36.59
Empagliflozin/metformin tablets 12.5mg/850mg (*Synjardy*) (Boehringer Ingelheim)	1 twice daily	£36.59 (28)	£36.59
Empagliflozin/metformin tablets 12.5mg/1000mg (*Synjardy*) (Boehringer Ingelheim)	1 twice daily	£36.59 (28)	£36.59
Canagliflozin/metformin tablets 50mg/850mg (*Vokanamet*) (Janssen-Cilag Ltd)	1 twice daily	£39.20 (30)	£36.59
Canagliflozin/metformin tablets 50mg/1000mg (*Vokanamet*) (Janssen-Cilag Ltd)	1 twice daily	£39.20 (30)	£36.59
Dapagliflozin/metformin tablets 5mg/850mg (*Xigduo*) (AstraZeneca UK Ltd)	1 twice daily	£36.59 (28)	£36.59
Dapagliflozin/metformin tablets 5mg/1000mg (*Xigduo*) (AstraZeneca UK Ltd)	1 twice daily	£36.59 (28)	£36.59
Canagliflozin tablets 100mg (*Invokana*) (Janssen-Cilag Ltd)	100mg daily	£39.20 (30)	£36.59
Canagliflozin tablets 300mg (*Invokana*) (Janssen-Cilag Ltd)	300mg daily	£39.20 (30)	£36.59
Dapagliflozin tablets 10mg (*Forxiga*) (AstraZeneca UK Ltd)	10mg daily	£36.59 (28)	£36.59
Empagliflozin tablets 10mg (*Jardiance*) (Boehringer Ingelheim)	10mg daily	£36.59 (28)	£36.59
Empagliflozin tablets 25mg (*Jardiance*) (Boehringer Ingelheim)	25mg daily	£36.59 (28)	£36.59
Metformin 850mg tablets (generic)	850mg twice daily	£1.94 (28)	£1.94
Metformin 500mg tablets (generic)	1000mg twice daily	£1.34 (28)	£5.36

PACEF Recommendation:

Empagliflozin/metformin tablets 5mg/ 850mg, 5mg/1000mg, 12.5mg/850mg and 12.5mg/1000mg (*Synjardy*) are designated GREEN and approved for use through the *Lincolnshire Joint Formulary* where a SGLT2 inhibitor is indicated in combination with metformin. Following the recent publication of the NICE clinical guideline on the treatment of type 2 diabetes, PACEF is in the process of reviewing local prescribing guidance. This will form the basis of a *PACE Bulletin* special to be issued early in the new year. Clinicians are reminded that SGLT2 inhibitors are a third line treatment option and that the European Medicines Agency is currently reviewing the SGLT2 class because of the risk of diabetic ketoacidosis associated with their use.

NEW PRODUCT ASSESSMENT: *MIDODRINE HYDROCHLORIDE 2.5MG AND 5MG TABLETS (BRAMOX)*

A new lower cost licensed formulation of midodrine 2.5mg and 5mg tablets (*Bramox*) is now available and preferred over unlicensed alternatives for the treatment of severe orthostatic hypotension. Changes to the NHS reimbursement price means that Lincolnshire CCGs can expect fortuitous savings of over £34,000pa.

Bramox is a new licensed tablet formulation of midodrine hydrochloride available as both 2.5mg and 5mg strengths. It holds a marketing authorisation for treatment of severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate; the treatment of other forms of

orthostatic hypotension would still be deemed to be off-license. The product has been licensed on the basis of bioequivalence data demonstrating equivalence to the European product, *Gutron,* which remains unlicensed in the UK.

Clinical evidence supporting the use of midodrine for orthostatic hypotension comes from two small scale, short duration randomised clinical trials that show that midodrine at a dose of 10mg three times daily increases standing blood pressure significantly more than placebo 1 hour after the dose is taken.

The cost of unlicensed midodrine preparations varies significantly dependent upon supplier. *Bramox* is being marketed at a price significantly lower than unlicensed alternatives. The Scottish Medicines Consortium (SMC) has recently approved *Bramox* for use in adults with severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate.

PACEF Recommendation

Midodrine hydrochloride 2.5mg and 5mg tablets *(Bramox)* are designated AMBER with shared care and approved for use through the *Lincolnshire Joint Formulary* for the treatment of orthostatic hypotension and vasovagal syncope. The NHS reimbursement price for midodrine 2.5mg and 5mg tablets in the *Drug Tariff* is now set at the *Bramox* price; this means that both open generic prescriptions and branded *Bramox* prescriptions will be reimbursed at the *Bramox* price. It is estimated that this will generate fortuitous savings across the four Lincolnshire CCGs of £34,249pa. Clinicians are advised to ensure that midodrine hydrochloride tablets 2.5mg and 5mg are supplied as *Bramox*; this can either be achieved by confirming with your local community pharmacist that *Bramox* will be supplied against generic prescriptions or by prescribing *Bramox* by brand. There is no longer any need for higher cost alternative brands unlicensed in the UK or unlicensed specials to be supplied against these prescriptions. A revised version of the midodrine shared care guideline is in preparation and will be published shortly.

NEW PRODUCT ASSESSMENT: *TAFLUPROST 15MCG/TIMOLOL 5MG PER ML PRESERVATIVE FREE SINGLE USE EYE DROPS (TAPTIQOM)*

Tafluprost 15mcg/timolol 5mg per ml preservative-free single use eye drops *(Taptiqom)* are designated AMBER without shared care and are preferred where a prostaglandin analogue/beta-blocker preservative-free eye preparation is indicated in the treatment of ocular hypertension or open-angle glaucoma.

Taptiqom is a new preservative free prostaglandin analogue (PGA) and beta-blocker (BB) combination eye drop licensed for the treatment of ocular hypertension or open-angle glaucoma insufficiently responsive to BBs or PGA alone. It contains tafluprost and timolol.

Tafluprost is a relatively marginal PGA in Lincolnshire and is prescribed infrequently. *Lincolnshire Formulary* recommendations, recently updated and re-published in *PACE Bulletin* Vol 9 No 6 (May 2015), advocate preparations containing latanoprost, bimatoprost and travoprost in combination with timolol first or second line. Where a preservative free PGA preparation is indicated, tafluprost is advocated second line after latanoprost.

A cost comparison of the only two preservative free PGA/BB preparations currently available reveals the following:

	Dose	Cost
Bimatoprost 300mcg/timolol 5mg per ml preservative-free single use eye drops (*Ganfort*) (Allergan)	1 drop into the affected eye(s) once daily in the morning or evening.	30 x 0.4ml £17.50
Tafluprost 15mcg/timolol 5mg per ml preservative-free single use eye drops *(Taptiqom)* (Santen)	1 drop into the affected eye(s) once daily.	30 x 0.3ml £14.50

PACEF Recommendation:
While *Taptiqom* is more expensive than preservative containing branded PGA/BB combination products, it is lower cost than the only alternative preservative-free PGA/BB combination eye drop currently available, *Ganfort.* As a result of this, tafluprost 15mcg/timolol 5mg per ml preservative-free single use eye drops *(Taptiqom)* are designated AMBER without shared care and are preferred through the Lincolnshire Joint Formulary where a PGA/BB preservative-free preparation is indicated. Prescribers are reminded that preservative free formulations should only be used in genuine cases of hypersensitivity to the preservative.

NAME CHANGE: *LITHIUM CARBONATE 250MG TABLETS (CAMCOLIT)*

The Medicines and Healthcare products Regulatory Agency (MHRA) have reported that lithium carbonate 250mg tablets previously known as *Camcolit* have been renamed as lithium carbonate Essential Pharma 250mg tablets. The strength and formulation remain the same. The higher strength modified release product *Camcolit* 400mg prolonged release tablets has not been rebranded.

Advice to prescribers

- All lithium should be prescribed by brand due to differing bioavailability between products.
- Patients on *Camcolit* 250mg tablets should be informed of the proprietary name change and lithium cards and lithium treatment booklets updated accordingly.

PACEF Recommendation
Review of prescribing data reveals that many prescriptions for lithium preparations are still prescribed generically despite a specific BNF caution around wide variation in bioavailability between preparations. Clinicians are urged to ensure that all lithium prescribing is brand specific. Clinicians are also reminded of the monitoring requirements for all patients taking lithium. Once the patient is stabilised, routine serum lithium monitoring should be done every three months with additional monitoring introduced if the patient develops significant intercurrent disease or there is a significant change in sodium level or fluid intake. Renal function, cardiac function and thyroid function should be monitored every 6 months.

RIVAROXABAN PRICE REDUCTION AND WITHDRAWAL OF REBATE SCHEME

Bayer have reduced the price of rivaroxaban (*Xarelto*) and discontinued the *Xarelto Rebate Scheme* from 1st December 2015. Fortuitous savings resulting from the price reduction across the Lincolnshire CCGs are likely to be in excess of £150,000pa.

An updated cost comparison of the newer oral anticoagulant drugs appears below:

	Dose	***Cost of 12 months treatment***
Apixaban 2.5mg tablets (*Eliquis*) (Bristol-Myers Squibb Pharmaceuticals Ltd)	2.5mg twice daily	£799.50 (28 day cost £61.50)
Apixaban 5mg tablets (*Eliquis*) (Bristol-Myers Squibb Pharmaceuticals Ltd)	5mg twice daily	£799.50 (28 day cost £61.50)
Dabigatran 150mg capsules (*Pradaxa)* (Boehringer Ingelheim Ltd)	150mg twice daily	£799.63 (28 day cost £61.51)
Dabigatran 110mg capsules (*Pradaxa*) (Boehringer Ingelheim Ltd)	110mg twice daily	£799.63 (28 day cost £61.51)
Edoxaban 30mg tablets (*Lixiana*) (Daiichi Sankyo)	30mg once daily	£764.40 (28 day cost £58.80)
Edoxaban 60mg tablets (*Lixiana*) (Daiichi Sankyo)	60mg once daily	£764.40 (28 day cost £58.80)
Rivaroxaban 20mg tablets (*Xarelto*) (Bayer plc)	20mg once daily	£655.20 (28 day cost £50.40)*

EAST MIDLANDS CARDIOVASCULAR STRATEGIC CLINICAL NETWORK, *MEDICINES AND YOUR KIDNEYS LEAFLET*

This month sees the launch of a patient information leaflet on the subject of *Medicines and Your Kidneys* launched by the East Midlands Cardiovascular Strategic Clinical Network. Copies of the leaflet and supporting resources are in the process of being distributed to practices. Patients who should receive a copy of the leaflet include those on ACE inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs and metformin.

Further information is available on the *Think Kidneys* website:
https://www.thinkkidneys.nhs.uk/

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

Crizotinib (*Xalkori*): *Risk of cardiac failure*

Crizotinib (*Xalkori*) is licensed to treat adults with previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer. There have been reports of severe, sometimes fatal, cases of cardiac failure in patients treated with crizotinib. A review by European medicines regulators of data from clinical trials and reports from clinical practice has concluded that this side effect is common (i.e. it occurs in between 1 in 10 and 1 in 100 patients who take crizotinib).

Advice for healthcare professionals:

- Monitor all patients receiving crizotinib therapy for signs and symptoms of heart failure (including dyspnoea, oedema, or rapid weight gain from fluid retention)
- Consider reducing the dose, or interrupting or stopping treatment if symptoms of heart failure occur

Vemurafenib (*Zelboraf*): *Risk of potentiation of radiation toxicity*

Vemurafenib (*Zelboraf*) is indicated as monotherapy for the treatment of adults with BRAF V600 mutation-positive unresectable or metastatic melanoma. A review of worldwide data by EU medicines regulators concluded that vemurafenib can potentiate radiation toxicity. These cases occurred in patients who received radiation before, during, or after treatment with vemurafenib. Most cases were confined to the skin, but some involved visceral organs and

resulted in a fatal outcome (including one case of radiation necrosis of the liver and two cases of radiation oesophagitis).

Advice for healthcare professionals:

- Vemurafenib should be used with caution when given before, during, or after radiotherapy and prescribers should be aware of the risk of potentiation of radiation toxicity.

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