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Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 11 Number 6 **March 2017**

What's new this month?

- **Tiotropium 10microgram inhalation powder (*Braltus*) plus delivery device (*Zonda* inhaler) is designated GREEN for use in adults as maintenance bronchodilator treatment to relieve the symptoms of COPD; it is approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. The product can be considered as bioequivalent with the *Spiriva Handihaler*; switching from the *Spiriva* product to *Braltus Zonda* is encouraged as part of the *Medicines Optimisation QIPP Programme* for 2017/18 (see page 3).**
- ***Fluenz Tetra* nasal spray is the preferred influenza vaccine in children and is designated GREEN and approved for use through the *Lincolnshire Joint Formulary*. *Fluarix Tetra* injection is a high cost quadrivalent inactivated influenza vaccine that is recommended for use in children, but has not been proven to be cost-effective in adults. Practices purchasing influenza vaccine for the influenza vaccination programme 2017/18 should continue to focus on lower cost trivalent inactivated vaccines for adults, such as inactivated influenza vaccine BP (Sanofi Pasteur), *Agrippal*, *Enzira*, *Imuvac* and *Influvac* (see page 5).**
- **Guanfacine *(Intuniv)* 1mg, 2mg, 3mg and 4mg modified release tablets for attention deficit hyperactivity disorder (ADHD) are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary* (see page 7).**
- **Eflornithine cream (*Vaniqa*) continues to be designated RED-RED for the treatment of facial hirsutism in female adolescents (aged 12 to 18 years) and adult women, even those with a diagnosis of Polycystic Ovary Syndrome (PCOS). However, in line with Specialised Services Circular 1417, *Primary care responsibilities in relation to prescribing and monitoring of hormone therapy for patients undergoing or having undergone gender dysphoria treatments* (March 2014), eflornithine cream (*Vaniqa*) is designated AMBER without shared care when initiated or recommended by a Gender Identity Clinic for patients undergoing or having undergone gender dysphoria treatments. PACEF recognise that eflornithine cream (*Vaniqa*) is not licensed for this indication (see page 8).**
- **Apremilast 10mg, 20mg and 30mg tablets (Otezla) are designated RED for the treatment of severe chronic plaque psoriasis as recommended by NICE TA 419 (November 2016) (see NICE Update below). Despite the fact that treatment with apremilast will be managed entirely through the ULH Dermatology service, primary care clinicians should remain vigilant to the risk of depression, suicidal thoughts or suicidal behaviour or the worsening of existing symptoms in patients taking this drug (see page 10).**
- **Following the publication of NICE TA 418, dapagliflozin can now be prescribed as triple therapy with metformin and a sulfonylurea. Dapagliflozin 5mg and**

10mg tablets (*Forxiga*) and dapagliflozin//metformin tablets 5mg/850mg and 5mg/1000mg (*Xigduo*) are designated GREEN and available for use through the *Lincolnshire Joint Formulary* within the context of NICE guidance and licensed indications (see page 10).

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SUMMARY OF PACEF DECISIONS: *JANUARY/FEBRUARY 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 adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or PUVA (psoralen and ultraviolet-A light).	RED Approved for inclusion in the *Lincolnshire Joint Formulary* for this indication.
Dapagliflozin 5mg and 10mg tablets (*Forxiga*) (AstraZeneca)	For use in adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* for all indications.
Dapagliflozin 5mg/metformin 850mg and 5mg/metformin 1000mg tablets (*Xigduo*) (AstraZeneca)	For use in adults with type 2 diabetes mellitus not controlled by metformin alone or by metformin in combination with insulin or other antidiabetic drugs,	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* for all indications.
Eflornithine 11.5% cream (*Vaniqa*) (Almirall)	Licensed for the treatment of facial hirsutism in female adolescents (aged 12 to 18 years) and adult women.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*;
Eflornithine 11.5% cream (*Vaniqa*) (Almirall)	For the treatment of facial hirsutism in patients undergoing or having undergone gender dysphoria treatments.	AMBER without shared care. Approved for inclusion in the *Lincolnshire Joint Formulary* subject to initiation or recommendation by a Gender Identity Clinic (GIC). *Vaniqa* is not licensed for this indication.
Fluarix Tetra inactivated quadrivalent influenza vaccine (GlaxoSmithKline)	Influenza immunisation	Not recommended for use in adults: RED-RED. Designated GREEN for use in children under 18 years. Approved for use through the *Lincolnshire Joint Formulary* solely for this indication
Fluenz Tetra nasal spray (AstraZeneca)	Influenza prophylaxis	GREEN Included in the *Lincolnshire Joint Formulary.* Not recommended for use in adults

		aged 18 years and over.
Guanfacine (Intuniv) 1mg, 2mg 3mg and 4mg modified release tablets (Shire)	For the treatment of Attention Deficit Hyperactivity Disorder in children aged 6 to 17 years when response to stimulants is inadequate or when stimulants are unsuitable or not tolerated.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*; exceptions may be granted subject to a successful Individual Funding Request.
Tiotropium 10microgram inhalation powder (*Braltus*) plus delivery device (*Zond*a inhaler) (Teva Ltd)	For use in adults as a maintenance bronchodilator treatment to relieve symptoms in patients with chronic obstructive pulmonary disease (COPD).	GREEN. Approved for inclusion in the *Lincolnshire Joint Fo*rmulary as a lower cost alternative to the *Spiriva Handihaler.*

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 Cathy Johnson on cathy.johnson@nhs.net or catherine.johnson@optum.com

Google searching can be a quick and effective way of finding back numbers of the *PACE Bulletin* relevant to a specific topic of interest. Searchers are advised to use the official version of the *Bulletin* available from the PACEF website rather than depend on a potentially unreliable draft or variant found through Google or an alternative search engine.
The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT and LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care.**

NEW DRUG ASSESSMENT: *TIOTROPIUM 10 MICROGRAM INHALATION POWDER (BRALTUS) PLUS DELIVERY DEVICE (ZONDA INHALER)*

Tiotropium 10microgram inhalation powder (*Braltus*) plus delivery device (*Zonda* inhaler) is designated GREEN for use in adults as maintenance bronchodilator treatment to relieve the symptoms of COPD; it is approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. The product can be considered as bioequivalent with the *Spiriva Handihaler*; product switching from the *Spiriva* product to *Braltus Zonda* is encouraged as part of the *Medicines Optimisation QIPP Programme* for 2017/18.

Teva have launched a new lower cost alternative to the tiotropium bromide 18 microgram inhalation device (*Spiriva Handihaler*) known as the *Braltus Zonda* inhaler. Due to a change in the convention on labelling of inhalational therapies, the *Braltus* brand is labelled with the delivered dose of tiotropium (10microgram) rather than tiotropium bromide (18microgram), but has been demonstrated to be equivalent dose for dose with the *Spiriva Handihaler.*

To gain a marketing authorisation, the *Braltus* product had to demonstrate bioequivalence to the originator brand (*Spiriva HandiHaler*). PACEF reviewed supporting evidence from a series of comparative studies, all of which demonstrated bioequivalence between the two

products in terms of both peak inspiratory flow and inhalation volume in healthy volunteers and in patients with a diagnosis of chronic obstructive pulmonary disease (COPD). *Braltus* is licensed for use in adults as maintenance bronchodilator treatment to relieve symptoms in COPD.

The delivery device for *Braltus*, the *Zonda* inhaler, is of very similar design to the *HandiHaler* and should be easy to use for those already experienced in using the *HandiHaler.* The mouthpiece is slightly longer than that of the *HandiHaler* enabling an easier grip in the mouth and a potentially better seal. The tiotropium powder for inhalation in *Braltus* is formulated into hard capsules similar to those used with the *HandiHaler*. *Braltus* capsules are clear and transparent enabling the patient to ensure that the complete dose has been inhaled. *Braltus* is only available in a 30 day pack with all packs containing a new *Zonda* device. Frequent replacement of the inhalation device reduces the need for regular cleaning and helps to reduce the associated risks of clogging and infection.

A cost comparison of the two products including a wider range of alternatives, reveals that *Braltus Zonda* is significantly cheaper than *Spiriva HandiHaler*.

Drug	**Daily dose**	**Cost (£) (doses)**
Tiotropium containing products		
***Braltus* 10mcg inhalation powder via *Zonda* delivery device (Teva)**	**Once daily**	**£25.80 (30)**
Spiriva 18mcg powder capsules (Boehringer Ingelheim)	Once daily	£33.50 (30) £67.00 (60)
Spiriva 18mcg powder capsules plus *HandiHaler* device (Boehringer Ingelheim)	Once daily	£34.87 (30)
Spiriva 2.5mcg per dose, oral solution via *Respimat* device (Boehringer Ingelheim)	5mcg (2 doses) once daily.	£23.00 (60)
Alternative long acting anti-muscarinics (LAMA)		
Aclidinium bromide 375mcg (*Eklira*) via *Genuair* device (AstraZeneca)	One dose twice daily	£28.60 (60)
Glycopyrronium bromide capsules 50mcg (*Seebri*) via *Breezhaler* (Novartis)	One dose once daily	£27.50 (30)
Umeclidinium 55mcg (*Incruse*) via *Ellipta* device (GlaxoSmithKline)	Once daily	£27.50 (30)

The estimated saving for the four Lincolnshire CCGs if all prescriptions for *Spiriva HandiHaler*, both generic and brand, were switched to *Braltus Zonda* is as follows:

CCG	**Annual saving assuming 100% switch from *Spiriva Handihaler***
Lincolnshire East CCG	£231,089
Lincolnshire West CCG	£190,200
South West Lincolnshire CCG	£116,538
South Lincolnshire CCG	£102,859
Lincolnshire	£640,686

<u>PACEF Recommendation</u>:
Tiotropium 10microgram inhalation powder (*Braltus*) plus delivery device (*Zonda* inhaler) is designated GREEN for use in adults as maintenance bronchodilator treatment to relieve the symptoms of COPD; it is approved for inclusion in the *Lincolnshire Joint Formulary* for this indication. The product can be considered as bioequivalent dose for dose with the *Spiriva Handihaler*; product switching from the *Spiriva* product to *Braltus Zonda* is encouraged as part of the *Medicines Optimisation QIPP Programme* for 2017/18. Assuming a 50% switch, the savings across

Lincolnshire will be close to £0.3Mpa. Although both products are equivalent, the strength of *Braltus* is quoted in terms of tiotropium content per capsule (10 microgram) rather than tiotropium bromide content (18 microgram in *Spiriva* capsules). This means that, regardless of whether these products are prescribed generically or by brand, there should be no confusion between the two at the dispensing stage with continuity of device and reduced risk of confusion assured. PACEF are aware that following a recent price reduction, the *Spiriva Respimat* device is currently the lowest cost option in this treatment area. However, advice from local respiratory specialists does not support the use of the *Respimat* as it requires a relatively high level of dexterity, strength and coordination both to prime the device and administer the dose; consequently the *HandiHaler* and, particularly, the *Zonda* device are preferred (see also *PACE Bulletin* Vol 10 No 16 (November 2016)).

REVIEW: *QUADRIVALENT INACTIVATED INFLUENZA VACCINES*

Fluarix Tetra* injection is a high cost quadrivalent inactivated influenza vaccine that is recommended for use in children, but has not been proven to be cost-effective in adults. Practices purchasing influenza vaccine for the influenza vaccination programme 2017/18 should continue to focus on lower cost trivalent inactivated vaccines for adults, such as inactivated influenza vaccine BP (Sanofi Pasteur), *Agrippal*, *Enzira*, *Imuvac* and *Influvac.

Influenza is highly infectious with a usual incubation period of one to three days. Flu immunisation is one of the most effective interventions we can provide to reduce harm from flu and pressures on health and social care services during the winter.

There are three types of influenza virus: A, B and C. Influenza A and influenza B are responsible for most clinical illness. A viruses cause outbreaks in most years and are the usual cause of epidemics. They live and multiply in wildfowl from where they can be transmitted to humans; they are also carried by other mammals. B viruses tend to cause less severe disease and smaller outbreaks and the burden of disease is mostly in children; they are predominantly found in humans. C viruses are responsible for minor respiratory illness only.

Most current influenza vaccines are trivalent, containing two subtypes of influenza A and one B virus. Quadrivalent vaccines with an additional B virus have been developed and the first authorised quadrivalent flu vaccine was made available for use in the UK in 2013. The use of quadrivalent flu vaccines containing a B strain from each of the two B strain lineages is expected to improve the matching of the vaccine to the circulating B strain(s). The B strain makes up 30% of flu cases worldwide. However, quadrivalent vaccines are on average nearly twice as expensive as trivalent vaccines. At present, it is also unlikely that there will be sufficient supply of quadrivalent vaccine produced each season to ensure everyone eligible for an influenza vaccine will be able to receive the quadrivalent type. The World Health Organisation (WHO) is encouraging all influenza vaccine producers to move to quadrivalent vaccines in the coming years and this is likely to resolve supply problems in the longer term. Because influenza B is relatively more common in children, the vaccines centrally purchased for the childhood vaccination programme in recent years have been quadrivalent preparations (*Fluenz Tetra* and *Fluarix Tetra*). The childhood programme should therefore contribute to better control of influenza B overall, by reducing transmission across the population.

A review of the range of influenza vaccines currently available on the NHS reveals the stark difference in price between the trivalent and quadrivalent inactivated vaccines, with *Fluarix Tetra*, the quadrivalent inactivated vaccine, costing nearly twice as much per dose as the widely prescribed trivalent alternatives:

Product	Manufacturer	Dose (adults unless stated)	Age restrictions	Cost (£)
Quadrivalent inactivated influenza vaccine				
Fluarix Tetra injection	GlaxoSmithKline	0.5ml by IM injection	Children under 3 years: not recommended	£9.94
Quadrivalent live attenuated vaccines				
Fluenz Tetra nasal spray	AstraZeneca UK	Children over 24 months: 0.1ml per nostril.	Adults18 years and over: not recommended.	Nasal spray, 0.2ml susp in single-use applicator, 10=£180.00. £18.00 per dose.
Trivalent inactivated vaccines				
Agrippal injection	Seqirus Vaccines Ltd	0.5ml by IM or deep SC inj.	Children under 6 months: not recommended	£5.85
Enzira injection	Pfizer Ltd	0.5ml by IM or deep SC inj	Children under 5 years: not recommended	£5.25
Imuvac injection	BGP Products	0.5ml by IM or deep SC inj	Children under 6 months: not recommended	£6.59
Inactivated Influenza Vaccine BP	Sanofi Pasteur	0.5ml by IM or deep SC inj.	Children under 6 months: not recommended	£6.59
Influvac injection	BGP Products Ltd	0.5ml by im or deep sc inj.	Children under 6 months: not recommended	£5.22
Intanza injection	Sanofi Pasteur	Over 60 years, 15 microgram by intradermal inj.	Adults under 60 years: not recommended	£9.05

Current advice in the *Lincolnshire Joint Formulary* states that:

'Fluarix Tetra should only be used in children aged 3 to 18 as defined in the influenza chapter of *Immunisation Against Infectious Disease* (chapter 19). There is no role for the product in older age groups and it should not be prescribed or administered to this group as part of the influenza vaccination programme'.

In response to practice requests, PACEF have reviewed this paragraph in preparation for the influenza vaccination programme 2017/18.

Advice quoted in *Immunisation Against Infectious Disease* (the Green Book) states that the:

"….JCVI (Joint Committee on Vaccinations and Immunisation) has advised that **all other things being equal**, quadrivalent inactivated vaccine is preferable to trivalent inactivated influenza vaccine"

Unfortunately, all other things are not equal as: (1) quadrivalent influenza inactivated vaccine is nearly double the cost of trivalent vaccine and (2) the cost-effectiveness of quadrivalent vaccination in adults compared to trivalent vaccination has not yet been established.

Use of the quadrivalent vaccine in adults is currently under review by Public Health England (PHE) and the JCVI who will be reviewing cost effectiveness in the adult high risk population.

Until a decision is made nationally around cost effectiveness of the quadrivalent vaccine with adult high-risk priority groups clearly defined, trivalent influenza vaccines should be preferred in the adult group.

PACEF Recommendation:
***Fluenz Tetra* nasal spray is the preferred influenza vaccine in children and is designated GREEN and approved for use through the *Lincolnshire Joint Formulary*. *Fluarix Tetra* injection is a high cost quadrivalent inactivated influenza vaccine that is recommended for use in children, but has not been proven to be cost-effective in adults. Practices purchasing influenza vaccine for the influenza vaccination programme 2017/18 should continue to focus on lower cost trivalent inactivated vaccines for adults, such as inactivated influenza vaccine BP (Sanofi Pasteur), *Agrippal*, *Enzira*, *Imuvac* and *Influvac.* All of these products are designated GREEN; *Fluarix Tetra* injection is only designated GREEN for use in children under 18. Any practices that have already placed orders for *Fluarix Tetra* for use in adults in preparation for the 2017/18 Influenza Season are asked to cancel these orders, where possible, and to re-order their preferred trivalent brand or generic.**

NEW DRUG ASSESSMENT: *GUANFACINE (INTUNIV) 1MG, 2MG, 3MG AND 4MG MODIFIED RELEASE TABLETS*

As a result of unresolved concerns over safety and uncertainty over cost effectiveness, guanfacine (*Intuniv*) 1mg, 2mg, 3mg and 4mg modified release tablets are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary*.

Guanfacine (*Intuniv*) is a selective alpha 2 – adrenergic receptor agonist licensed for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents aged 6-17 years for whom stimulants are either not suitable, not tolerated or have been shown to be ineffective. Treatment must be initiated under the supervision of an appropriate specialist in childhood and/or adolescent behavioural disorders with comprehensive pre-treatment screening and on-going monitoring

PACEF reviewed the results of four placebo controlled trials all of which demonstrated the effectiveness of guanfacine in patients within the licensed age range. However, despite the inclusion of atomoxetine in one trial as an internal reference vs placebo, there are no comparator trials directly comparing guanfacine with any other active ADHD treatment. All four of the RCTs had differing inclusion criteria and were of short duration (maximum 13 weeks). High placebo response rates and high dropout rates also made interpretation of the results difficult. People with current psychiatric co-morbidity were excluded from the trials, so the trial population may not be truly reflective of the patient population seen in clinical practice.

Potentially serious adverse events have also been identified including weight gain, cognitive impairment (i.e. potential impaired learning, delay of cognitive development) and cardiac effects (i.e. lowering of BP and heart rate, prolongation of QT interval). A number of clinically significant drug interactions have also been identified that are likely to be encountered in practice.

A cost comparison reveals that guanfacine modified release tablets are comparable in cost to atomoxetine capsules and 4mg/ml oral solution. Cost effectiveness has not yet been established with different authorities publishing different advice. The Scottish Medicines Consortium considers the economic case to be demonstrated while the Welsh New

Medicines Group state that the case for cost effectiveness has not been proven. A recent *Drug and Therapeutics Bulletin* (DTB) published in May 2016 concluded that:

> "Given the lack of comparative data with other drugs for ADHD and concerns over the risk of sedation, cardiovascular effects and obesity, we believe there is a very limited role for guanfacine in the management of ADHD. Until there is further evidence on long term efficacy and safety it should only be prescribed and monitored by specialists in the management of ADHD"

PACEF Recommendation:
Following review of guanfacine (*Intuniv*) modified release tablets, PACEF remain unconvinced as to the effectiveness, safety and cost effectiveness of the product. As a result, guanfacine (*Intuniv*) 1mg, 2mg, 3mg and 4mg modified release tablets are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary*; exceptions may be granted subject to a successful Individual Funding Request.

REVIEW: *EFLORNITHINE 11.5% CREAM (VANIQA)*

This is an updated version of a Rapid Drug Assessment originally published in *PACE Bulletin* Vol 6 No 3 (January 2012).

Eflornithine cream (*Vaniqa*) continues to be designated RED-RED for the treatment of facial hirsutism in female adolescents (aged 12 to 18 years) and adult women, even those with a diagnosis of Polycystic Ovary Syndrome (PCOS). However, in line with Specialised Services Circular 1417, *Primary care responsibilities in relation to prescribing and monitoring of hormone therapy for patients undergoing or having undergone gender dysphoria treatments* (March 2014), eflornithine cream (*Vaniqa*) is designated AMBER without shared care when initiated or recommended by a Gender Identity Clinic for patients undergoing or having undergone gender dysphoria treatments. PACEF recognise that eflornithine cream (*Vaniqa*) is not licensed for this indication.

Eflornithine 11.5% cream (*Vaniqa)* was the first topical product licensed for the treatment of facial hirsutism in female adolescents (aged 12 to 18 years) and adult women. PACEF reviewed current guidance following a request from ULH Dermatologists for the product to be available for the treatment of facial hirsutism in women who have been diagnosed with Polycystic Ovary Syndrome (PCOS),

Evidence from two identically designed randomised controlled trials showed that topical eflornithine treatment resulted in a significant reduction of visible facial hair in about one-third of women. However this improvement was not maintained and hair growth approached pre-treatment levels within 8 weeks of discontinuation of therapy.

Eflornithine is well tolerated with the most common adverse effects documented as burning, stinging and tingling of the skin. There is a theoretical risk that long-term use may result in skin atrophy, but published trials have been too short in duration to assess this risk. Patients who respond to topical eflornithine are likely to require ongoing therapy, so uncertainty over long-term safety remains a significant issue.

Co-cyprindiol is the only other product licensed for the treatment of hirsutism. Metformin is an alternative possibility in patients with polycystic ovary syndrome (POS). Eflornithine cream is considerably more expensive than co-cyprindiol with an annual cost of £341.22 per

year (based on an expected usage of 30g or half a 60g tube per month) compared to £22.80pa for generic co-cyprindiol.

A Specialised Services Circular published in March 2014 defines primary care responsibilities in relation to the prescribing and monitoring of hormone therapy for patients undergoing or having undergone gender dysphoria treatments. This circular provides clarity to GPs on the roles and responsibilities of the Gender Identity Clinics (GICs) and the role GPs have in the ongoing provision and monitoring of the requested endocrine therapy. Within this Circular a number of typical drugs recommended by GICs for prescribing by GPs are identified; these include: oestradiol and testosterone preparations, gonadotrophin releasing hormone analogues and depilatory agents such as topical eflornithine (*Vaniqa*).

The Circular contains a link to a publication from the Royal College of Psychiatrists (RCPsych) published in October 2013 which provides more detail on the treatments provided, including those for the removal of hair. As a consequence of the surgical interventions and hormonal therapies associated with gender dysphoria treatments, androgen ablation will often not totally prevent hair growth and other methods of hair removal may be necessary. Shaving and waxing are widely used but their effect is temporary. The guidance suggests using more permanent methods of hair removal including electrolysis, laser hair removal and eflornithine cream (*Vaniqa*). It must be emphasized that *Vaniqa* is not licensed for this indication and that there is no published evidence to support its use in men.

PACEF Recommendation:
PACEF are concerned about the limited efficacy and long-term safety of eflornithine cream (*Vaniqa*). Only a third of women respond to treatment and hair growth approaches pre-treatment levels within 8 weeks of discontinuation. As a result of this, eflornithine cream (*Vaniqa*) continues to be designated RED-RED for the treatment of facial hirsutism in female adolescents (aged 12 to 18 years) and adult women, even those with a diagnosis of Polycystic Ovary Syndrome (PCOS). However, in line with Specialised Services Circular 1417, *Primary care responsibilities in relation to prescribing and monitoring of hormone therapy for patients undergoing or having undergone gender dysphoria treatments* (March 2014), eflornithine cream (*Vaniqa*) is designated AMBER without shared care when initiated or recommended by a Gender Identity Clinic for patients undergoing or having undergone gender dysphoria treatments. PACEF recognise that eflornithine cream (*Vaniqa*) is not licensed for this indication.

Reference:
Specialised Services Circular, *Primary care responsibilities in relation to the prescribing and monitoring of hormone therapy for patients undergoing or having undergone gender dysphoria treatments* (SSC1417) (26th March 2014).

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA), *DRUG SAFETY UPDATE* (DECEMBER 2016)

Spironolactone and renin-angiotensin system drugs in heart failure: risk of potentially fatal hyperkalaemia – clarification

The MHRA have clarified advice issued in the *Drug Safety Update* from February 2016 on the concomitant use of spironolactone and renin-angiotensin system drugs in patients with heart failure.

Concomitant use of spironolactone with an ACEI or ARB increases the risk of severe hyperkalaemia, particularly in patients with marked renal impairment, and should be used

with caution. The same advice applies for concomitant use of the aldosterone antagonist eplerenone with an ACEI or ARB in heart failure.

Monitoring of blood electrolytes is essential in patients co-prescribed a potassium-sparing diuretic and an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) for heart failure. Concomitant use of spironolactone with an ACEI or ARB is not routinely recommended because of the risks of severe hyperkalaemia, particularly in patients with marked renal impairment.

MEDICINES AND HEALTHCARE REGULATORY AGENCY: *DRUG SAFETY UPDATE* (JANUARY 2017)

Apremilast (Otezla): Risk of suicidal thoughts and behaviour

Apremilast (*Otezla*) is phosphodiesterase-type-4 inhibitor for the treatment of moderate to severe chronic plaque psoriasis or active psoriatic arthritis in adults who have not responded to other systemic treatments. There is an increased risk that some patients may experience psychiatric symptoms with apremilast, including depression and suicidal thoughts. Stop treatment if the patient has new psychiatric symptoms or if existing symptoms worsen.

Depression, suicidal thoughts, and suicidal behaviours are more common in patients with psoriasis or psoriatic arthritis than in the general population. Clinical trials and post-marketing experience (including reports to the Yellow Card scheme) have recorded serious psychiatric symptoms, including depression, suicidal thoughts, and suicidal behaviours. Suicidal thoughts and behaviours have been reported in patients with no previous history of depression. A review of the evidence from clinical trials and post-marketing cases has suggested a causal association between apremilast and suicidal thoughts and suicidal behaviour. These events are reported to occur uncommonly, with an estimated frequency of between 1 in 1000 to 10 in 1000 patients taking apremilast.

PACEF comment

Apremilast 10mg, 20mg and 30mg tablets (*Otezla*) are designated RED for the treatment of severe chronic plaque psoriasis as recommended by NICE TA 419 (November 2016) (see NICE Update below). Despite the fact that treatment with apremilast will be managed entirely through the ULH Dermatology service, primary care clinicians should remain vigilant to the risk of depression, suicidal thoughts or suicidal behaviour or the worsening of existing symptoms in patients taking this drug.

NICE TECHNOLOGY APPRAISAL TA418: *DAPAGLIFLFLOZIN IN TRIPLE THERAPY FOR TREATING TYPE 2 DIABETES* (NOVEMBER 2016)

Dapagliflozin in a triple therapy regimen in combination with metformin and a sulfonylurea is recommended as an option for treating type 2 diabetes in adults.

Notes

Current local guidance on the use of sodium-glucose co-transporter 2 (SGLT2) inhibitors, such as dapagliflozin, has been in line with NICE guidance and the licensed indications of each product. The additional approval of dapagliflozin as an option for triple therapy in combination with metformin and a sulfonylurea means that all three of the SGLT2 inhibitors are approved as treatment options for monotherapy, dual and triple therapy in combination with certain drugs.

The table below has been updated to include all new NICE recommendations and licensed indications:

	Canagliflozin (*Invokana*)	**Dapagliflozin (*Forxiga*)**	**Empagliflozin (*Jardiance*)**
Licensed indications	In adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin,	In adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin,	In adults with type 2 diabetes mellitus to improve glycaemic control as monotherapy or in combination with other glucose-lowering medicinal products including insulin,
NICE TA	√	√	√
Monotherapy	√	√	√
Dual therapy with metformin	√	√	√
Triple therapy Metformin + sulfonylurea	√	√	√
Triple therapy Metformin + pioglitazone	√	X	√
With insulin With or without other antidiabetic drugs	√	√	√
Use in renal impairment	Should not be initiated in patients whose eGFR<60ml/min/1.73 m2. In patients tolerating canagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m2, the dose of should be adjusted to or maintained at 100 mg once daily. Canagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m2.	Not recommended eGFR<60ml/min/1.73 m2	Should not be initiated in patients whose eGFR<60ml/min/1.73 m2. In patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min/1.73 m2, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Empagliflozin should be discontinued when eGFR is persistently below 45 ml/min/1.73 m2.
Available with metformin	√ Canagliflozin/metformin 50mg/850mg & 50mg/1g (*Vokanamet*)	√ Dapagliflozin /metformin 5mg/850mg & 5mg/1g (*Xigduo*)	√ Empagliflozin/metformin 5mg/850mg, 5mg/1g, 12.5mg/850mg & 12.5mg /1g (Synjardy)
Dose range	100mg daily increasing to 300mg daily if required	10mg once daily, lower 5mg dose may be needed if used with insulin or sulfonylureas	10mg once daily increasing to 25mg if necessary.

A cost comparison reveals that all of the SGLT2 inhibitors are identically priced; all of the agents are available as single component products and in combination with metformin.

Product	**Dose**	**Cost (£)**	**Cost (£) 28 days**
Canagliflozin 100mg (*Invokana*) (Janssen-Cilag)	100mg once daily	£39.20 (30)	£36.59
Canagliflozin 300mg	300mg once daily	£39.20 (30)	£36.59

(*Invokana*) (Janssen-Cilag)			
Canagliflozin 50mg/metformin 850mg (*Vokanamet*) (Janssen-Cilag)	One twice daily	£39.20 (30)	£36.59
Canagliflozin 50mg/metformin 1000mg (*Vokanamet*) (Janssen-Cilag)	One twice daily	£39.20 (30)	£36.59
Dapagliflozin 10mg (Forxiga) (AstraZeneca)	10mg once daily	£36.59 (28)	£36.59
Dapagliflozin 5mg (Forxiga) (AstraZeneca)	5mg once daily (consider lower dose if used in combination with insulin or sulfonylurea).	£36.59 (28)	£36.59
Dapagliflozin 5mg/metformin 850mg (*Xigduo*) (AstraZeneca)	One twice daily	£36.59	£36.59
Dapagliflozin 5mg/metformin 1000mg (*Xigduo*) (AstraZeneca)	One twice daily	£36.59	£36.59
Empagliflozin 10mg (*Jardiance*) (Boehringer Ingelheim)	10mg once daily	£36.59	£36.59
Empagliflozin 25mg (*Jardiance*) (Boehringer Ingelheim)	25mg once daily Usual dose 10mg increase to 25mg if necessary	£36.59	£36.59
Empagliflozin 5mg/metformin 850mg (Synjardy) (Boehringer Ingelheim)	One twice daily	£36.59	£36.59
Empagliflozin 5mg/metformin 1000mg (Synjardy) (Boehringer Ingelheim)	One twice daily	£36.59	£36.59
Empagliflozin 12.5mg/metformin 850mg (Synjardy) (Boehringer Ingelheim)	One twice daily	£36.59	£36.59
Empagliflozin 12.5mg/metformin 1000mg (Synjardy) (Boehringer Ingelheim)	One twice daily	£36.59	£36.59

PACEF Recommendation:

Dapagliflozin 5mg and 10mg tablets (*Forxiga*) and dapagliflozin//metformin tablets 5mg/850mg and 5mg/1000mg (*Xigduo*) are designated GREEN and available for use through the *Lincolnshire Joint Formulary* within the context of NICE guidance and licensed indications. Following the publication of NICE TA 418, dapagliflozin can now be prescribed as triple therapy with metformin and a sulfonylurea.

NICE UPDATE

NICE Technology Appraisal	Guidance	PACEF Recommendation
TA410 *Talimogene laherparepvec for treating unresectable metastatic melanoma* (September 2016)	Talimogene laherparepvec is recommended, in adults, as an option for treating unresectable, regionally or distantly metastatic (Stage IIIB, IIIC or IVM1a) melanoma that has not spread to bone, brain, lung or other internal organs, only if treatment with systemically administered immuno-therapies is not suitable and the company provides talimogene laherparepvec with the discount agreed in the patient access scheme.	Talimogene laherparepvec injection (*Imlygic*) is designated RED for this indication. It is already approved for use through the *Lincolnshire Joint Formulary.*
TA411 *Necitumumab for untreated advanced or metastatic squamous non-small-cell lung cancer* (September 2016)	Necitumumab, in combination with gemcitabine and cisplatin, is not recommended within its marketing authorisation for adults with locally advanced or metastatic epidermal growth factor receptor (EGFR)-expressing squamous non-small-cell lung cancer that has not been treated with chemotherapy. .	Necitumumab injection (*Portrazza*) is designated RED-RED and not approved for inclusion in the *Lincolnshire Joint Formulary*.
TA412 *Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases* (September 2016)	Radium-223 dichloride is recommended as an option for treating hormone relapsed prostate cancer, symptomatic bone metastases and no known visceral metastases in adults, only if: they have already had docetaxel or docetaxel is contraindicated or is not suitable for them.	Radium-223 dichloride 1100kBq/ml solution for injection (*Xofigo*) is designated RED for this indication and approved for use through the *Lincolnshire Joint Formulary*.
TA413 *Elbasvir-grazoprevir for treating chronic hepatitis C* (October 2016)	Elbasvir-grazoprevir is recommended as an option for treating genotype 1 or 4 chronic hepatitis C in adults.	Elbasvir-grazoprevir is designated RED and approved for use through the *Lincolnshire Joint Formulary.*
TA414: *Cobimetinib in combination with vemurafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma* (October 2016)	Cobimetinib in combination with vemurafenib is not recommended within its marketing authorisation for treating unresectable or metastatic melanoma in adults with a BRAF V600 mutation.	Cobimetinib 20mg tablets (*Cotellic*) is designated RED-RED and not approved for use through the *Lincolnshire Joint Formulary*
TA415: *Certolizumab pegol for treating rheumatoid arthritis after inadequate response to a TNF-alpha inhibitor* (October 2016)	Certolizumab pegol, in combination with methotrexate, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other disease-modifying antirheumatic drugs (DMARDs) including at least 1 tumour necrosis factor-alpha (TNF-alpha) inhibitor, only if: disease activity is severe and rituximab is contraindicated or not tolerated and the company provides certolizumab pegol with the agreed patient access scheme. Certolizumab pegol, as monotherapy, is recommended as an option for treating active rheumatoid arthritis in adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF-alpha inhibitor, only if: disease activity is severe and rituximab therapy cannot be given because methotrexate is contraindicated or not tolerated and the company provides certolizumab pegol with the agreed patient access scheme. Continue treatment only if there is at least a moderate response measured	Certolizumab pegol injection (*Cimzia*) is already designated RED and approved for use through the *Lincolnshire Joint Formulary* in accordance with NICE TAs 186,375 and 383. It is now designated as RED for the treatment of RA after inadequate response to a TNF-alpha inhibitor.

	using European League Against Rheumatism (EULAR) criteria at 6 months. After an initial response within 6 months, withdraw treatment if at least a moderate EULAR response is not maintained.	
TA416: *Osimertinib for treating locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer* (October 2016)	Osimertinib is recommended as an option for use within the Cancer Drugs Fund for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer in adults whose disease has progressed only: after first-line treatment with an EGFR tyrosine kinase inhibitor and if the conditions in the managed access agreement for osimertinib are followed.	Osimertinib 40mg and 80mg tablets (*Tagrisso*) are designated RED for this indication and approved for use through the *Lincolnshire Joint Formulary.*
TA417: *Nivolumab for previously treated advanced renal cell carcinoma* (November 2016)	Nivolumab is recommended, within its marketing authorisation, as an option for previously treated advanced renal cell carcinoma in adults, when the company provides nivolumab with the discount agreed in the patient access scheme.	Nivolumab 10mg/ml concentrate for solution for infusion (*Opdivo*) is already approved for use through the *Lincolnshire Joint Formulary* designated RED in line with NICE TA384 (treatment of advanced melanoma) and TA400 (in combination with ipilimumab for the treatment of advanced melanoma). It is now designated RED for previously treated advanced renal cell carcinoma.
TA419: *Apremilast for treating moderate to severe plaque psoriasis* (November 2016)	Apremilast is recommended as an option for treating chronic plaque psoriasis in adults whose disease has not responded to other systemic therapies, including ciclosporin, methotrexate and PUVA (psoralen and ultraviolet-A light), or when these treatments are contraindicated or not tolerated, only if: • the disease is severe, as defined by a total Psoriasis Area Severity Index (PASI) of 10 or more and a Dermatology Life Quality Index (DLQI) of more than 10. • treatment is stopped if the psoriasis has not responded adequately at 16 weeks; an adequate response is defined as a 75% reduction in the PASI score (PASI 75) from when treatment started or a 50% reduction in the PASI score (PASI 50) and a 5-point reduction in DLQI from start of treatment. • the company provides apremilast with the discount agreed in the patient access scheme.	Apremilast 10mg, 20mg and 30mg tablets (*Otezla*) are designated RED for this indication and are approved for use through the *Lincolnshire Joint Formulary.*
TA421 *Everolimus with exemestane for treating advanced breast cancer after endocrine therapy* (December 2016)	Everolimus, in combination with exemestane, is recommended within its marketing authorisation, as an option for treating advanced human epidermal growth factor receptor 2 (HER2)-negative, hormone-receptor-positive breast cancer in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor.	Everolimus 2.5mg, 5mg and 10mg tablets (*Afinitor*) are designated RED and approved for use for this indication through the *Lincolnshire Joint Formulary. Afinitor* should be prescribed by brand for this indication to avoid confusion with other brands for other indications (e.g. everolimus 250, 500 and 750 microgram tablets (*Certican*) for prophylaxis of organ rejection following liver or kidney transplant.)
TA422 *Crizotinib for previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer* (December 2016)	Crizotinib is recommended, within its marketing authorisation, as an option for previously treated anaplastic lymphoma kinase-positive advanced non-small cell	Crizotinib 200mg and 250mg capsules (*Xalkori)* are designated RED and approved for use for this indication through the *Lincolnshire Joint*

	lung cancer in adults.	*Formulary*.
TA423 *Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens* (December 2016)	Eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when: • it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).	Eribulin 0.44mg/ml solution for injection (*Halaven*) is designated RED and approved for use for this indication through the *Lincolnshire Joint Formulary*.
TA424 *Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer* (December 2016)	Pertuzumab, in combination with trastuzumab and chemotherapy, is recommended, within its marketing authorisation, as an option for the neoadjuvant treatment of adults with human epidermal growth factor receptor 2 (HER2)-positive breast cancer; that is, in patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence.	Pertuzumab 420mg concentrate for solution for infusion (*Perjeta*) is designated RED and approved for use for this indication through the *Lincolnshire Joint Formulary.*
TA425 *Dasatinib, nilotinib and high-dose imatinib for treating imatinib-resistant or intolerant chronic myeloid leukaemia* (December 2016)	Dasatinib and nilotinib are recommended as options for treating only chronic or accelerated-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults, if: they cannot have imatinib, or their disease is imatinib-resistant and the companies provide the drugs with the discounts agreed in the relevant patient access schemes. High-dose imatinib (that is 600 mg in the chronic phase or 800 mg in the accelerated and blast-crisis phases) is not recommended for treating Philadelphia-chromosome-positive chronic myeloid leukaemia in adults whose disease is imatinib-resistant.	Dasatinib 20mg, 50mg, 80mg, 100mg and 140mg tablets (*Sprycel*) are designated RED for this indication and approved for use through the *Lincolnshire Joint Formulary*. Nilotinib 150mg and 200mg capsules (*Tasigna*) are designated RED for this indication and approved for use through the *Lincolnshire Joint Formulary.* Imatinib 100mg and 400mg tablets (*Glivec*) are designated RED-RED and are not available through the *Lincolnshire Joint Formulary* for this indication.
TA426 *Dasatinib, nilotinib and imatinib for untreated chronic myeloid leukaemia* (December 2016)	Imatinib is recommended as an option for untreated, chronic-phase Philadelphia-chromosome-positive chronic myeloid leukaemia in adults. Dasatinib and nilotinib are recommended, within their marketing authorisations, as options for untreated chronic-phase Philadelphia chromosome-positive chronic myeloid leukaemia in adults.	Imatinib 100mg and 400mg tablets (*Glivec*) are designated RED and are approved for use through the *Lincolnshire Joint Formulary* for this indication. Dasatinib 20mg, 50mg, 80mg, 100mg and 140mg tablets (*Sprycel*) are designated RED for this indication and approved for use through the *Lincolnshire Joint Formulary*. Nilotinib 150mg and 200mg capsules (*Tasigna*) are designated RED for this indication and approved for use through the *Lincolnshire Joint Formulary.*
TA427 *Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib* (January 2017)	Pomalidomide, in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib, only when the company provides pomalidomide with the discount agreed in the patient access scheme.	Pomalidomide 1mg, 2mg, 3mg and 4mg capsules (*Imnovid*) are designated RED and are approved for use through the *Lincolnshire Joint Formulary* for this indication.
TA428 *Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy* (January 2017)	Pembrolizumab is recommended as an option for treating locally advanced or metastatic PD-L1-positive non-small-cell lung cancer in adults who have had at least one chemotherapy (and targeted treatment if they have an epidermal growth factor receptor [EGFR]- or anaplastic lymphoma kinase [ALK]-positive tumour), only if: pembrolizumab is stopped at 2 years of	Pembrolizumab 50mg powder for concentrate for solution for infusion (*Keytruda*) is designated RED and approved for use through the *Lincolnshire Joint Formulary* for this indication.

	uninterrupted treatment and no documented disease progression, and the company provides pembrolizumab with the discount agreed in the patient access scheme revised in the context of this appraisal.	
TA429 *Ibrutinib for previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation* (January 2017)	Ibrutinib alone is recommended within its marketing authorisation as an option for treating chronic lymphocytic leukaemia in adults: who have had at least 1 prior therapy or who have a 17p deletion or TP53 mutation, and in whom chemo-immunotherapy is unsuitable and only when the company provides ibrutinib with the discount agreed in the patient access scheme.	Ibrutinib 140mg capsules (*Imbruvica*) are designated RED and are approved for use through the *Lincolnshire Joint Formulary* for this indication. Ibrutinib was previously approved for use through the New Cancer Drugs Fund.
TA430 *Sofosbuvir–velpatasvir for treating chronic hepatitis C* (January 2017)	Sofosbuvir–velpatasvir is recommended as an option for treating chronic hepatitis C in adults.	Sofosbuvir/velpatasvir 400mg/100mg tablets (*Epclusa*) are designated RED and approved for use through the *Lincolnshire Joint Formulary* for this indication.
TA431 *Mepolizumab for treating severe refractory eosinophilic asthma* (January 2017)	Mepolizumab, as an add-on to optimised standard therapy, is recommended as an option for treating severe refractory eosinophilic asthma in adults, only if: the blood eosinophil count is 300 cells/microlitre or more in the previous 12 months and the person has agreed to and followed the optimised standard treatment plan and has had 4 or more asthma exacerbations needing systemic corticosteroids in the previous 12 months or has had continuous oral corticosteroids of at least the equivalent of prednisolone 5 mg per day over the previous 6 months and the company provides the drug with the discount agreed in the patient access scheme. At 12 months of treatment: stop mepolizumab if the asthma has not responded adequately or continue treatment if the asthma has responded adequately and assess response each year. An adequate response is defined as: at least 50% fewer asthma exacerbations needing systemic corticosteroids in those people with 4 or more exacerbations in the previous 12 months or a clinically significant reduction in continuous oral corticosteroid use while maintaining or improving asthma control.	Mepolizumab 100mg solution for injection (*Nucala*) is designated RED and approved for use through the *Lincolnshire Joint Formulary* for this indication. It will only be prescribed through tertiary centres.

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