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

Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 10; Number 10 **July 2016**

What's new this month?

- **Two new branded pregabalin capsule formulations have recently been launched, *Alzain* and *Pregabalin Zentiva*. Pregabalin capsules (*Alzain*) are now the lowest cost pregabalin preparation and are approved for use through the *Lincolnshire Joint Formulary* designation GREEN; all prescribing should be by brand. *Pregabalin Zentiva* capsules are comparably priced with *Lyrica* and should not be prescribed; designation RED-RED (see page 2).**
- **When prescribing pregabalin for the treatment of anything other than central or peripheral neuropathic pain, pregabalin should be prescribed as a lower cost brand, specifically as *Alzain* or *Rewisca*. Open generic scripts for pregabalin are still reimbursed at the higher *Lyrica* price; only branded prescribing of the preferred lower cost products will reduce prescribing costs (see page 2).**
- **There is a significant difference in cost between the premium price branded tramadol/paracetamol combination product (*Tramacet*) and the components prescribed separately. Prescribers are advised to review all patients on *Tramacet* and *Tramacet Effervescent* with a view to prescribing paracetamol, and tramadol as separate components wherever possible. Tramadol hydrochloride 37.5mg/paracetamol 325mg tablets (*Tramacet*) and tramadol hydrochloride 37.5mg/paracetamol 325mg effervescent tablets (*Tramacet Effervescent*) are designated RED-RED. Prescribing tramadol as generic 50mg capsules is significantly lower cost than any of the once or twice daily modified release preparations such as *Zamadol SR*, *Zydol SR*, *Zamadol 24 hour* and *Zydol XL* (see page 5).**
- **The MHRA have highlighted again the risk of diabetic ketoacidosis in patients taking the SGLT2 inhibitors, canagliflozin, dapagliflozin and empagliflozin (see page 7).**
- **Meprobamate 400mg tablets are due to be withdrawn at the end of the year (see page 11).**
- **Smoking or a naked flame can cause patients' dressings or clothing to catch fire when being treated with a paraffin-based emollient that is in contact with their dressing or clothing. *Eumocream* (glycerol 5% cream) has been approved for inclusion in the *Lincolnshire Joint Formulary* designation GREEN for those considered to be at risk of conflagration from paraffin containing emollients and requiring a paraffin-free alternative (see page 11).**
- **The European Medicines Agency has started a review of canagliflozin after an increase in amputations, mostly toes, was observed in an ongoing clinical trial called CANVAS. At this stage in the trial, there are cases of lower limb amputation in both the canagliflozin and the placebo groups, although the incidence is higher in the canagliflozin groups. No increase in such amputations has been seen in 12 other completed canagliflozin trials. Healthcare professionals should ensure that diabetic patients are aware of the importance of routine footcare to avoid cuts or sores of the feet and to treat them promptly should they occur to prevent infection and ulceration. Patients at increased risk of amputation (such as those who have already had a previous amputation) should be carefully monitored. Doctors may consider stopping canagliflozin in patients who develop significant foot problems (see page 12).**

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Page 12 **European Medicines Agency, *Review of canagliflozin* (15th April 2016).**

SUMMARY OF PACEF DECISIONS: *May 2016 Update*

Device, Dressing or Drug	Indication(s)	Traffic Light and *Joint Formulary* Status
Eumocream (glycerol 5% cream) (GlaxoSmithKline)	A glycerol based emollient for the treatment of dry or flaky skin conditions including eczema and dermatitis.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* for those considered to be at risk of conflagration from paraffin containing emollients and requiring a paraffin-free alternative.
Meprobamate 400mg tablets	For short-term use in anxiety	RED-RED Not included in the *Lincolnshire Joint Formulary.*
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (*Alzain*) (Dr Reddy's Laboratories UK Ltd)	For use as adjunctive therapy in adults with partial seizures with or without secondary generalisation and for the treatment of Generalised Anxiety Disorder (GAD) in adults.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* within licensed indications only.
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (*Rewisca)* (Consilient Health Ltd)	For use as adjunctive therapy in adults with partial seizures with or without secondary generalisation and for the treatment of Generalised Anxiety Disorder (GAD) in adults.	GREEN Approved for inclusion in the *Lincolnshire Joint Formulary* within licensed indications only.
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (*Lecaent*) (Actavis UK Ltd)	For use as adjunctive therapy in adults with partial seizures with or without secondary generalisation and for the treatment of Generalised Anxiety Disorder (GAD) in adults.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (*Pregabalin Zentiva)* (Zentiva)	For use as adjunctive therapy in adults with partial seizures with or without secondary generalisation and for the treatment of Generalised Anxiety Disorder (GAD) in adults.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*
Tramadol hydrochloride 37.5mg/paracetamol 325mg tablets (*Tramacet*) (Grunenthal)	For moderate to severe pain	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*
Tramadol hydrochloride 37.5mg/paracetamol 325mg effervescent tablets (*Tramacet Effervescent*) (Grunenthal)	For moderate to severe pain	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*

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

Two new branded pregabalin capsule formulations have recently been launched, *Alzain* and *Pregabalin Zentiva*. Pregabalin capsules (*Alzain*) are now the lowest cost pregabalin preparation and are approved for use through the *Lincolnshire Joint Formulary* designation GREEN; all prescribing should be by brand. *Pregabalin Zentiva* capsules are comparably priced with *Lyrica* and should not be prescribed; designation RED-RED.

The table below compares the marketing authorisations for the newer branded formulations of pregabalin with the originator brand, *Lyrica*. At present, *Lyrica* is the only pregabalin preparation with a marketing authorisation for peripheral and central neuropathic pain. Current guidance from the NHSE advocates prescribing *Lyrica* by brand for neuropathic pain and only prescribing the newer preparations within license (i.e. for epilepsy and GAD only).

Authorised indications

	Licensed indications
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (*Alzain*, Dr Reddy's Laboratories UK Ltd), (*Lecaent* , Actavis UK Ltd) (Rewisca, Consilient Health Ltd) , (*Pregabalin Zentiva*, Zentiva)	*Epilepsy* As adjunctive therapy in adults with partial seizures with or without secondary generalisation. *Generalised Anxiety Disorder* For the treatment of Generalised Anxiety Disorder (GAD) in adults.
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (*Lyrica*, Pfizer)	*Epilepsy* *A*s adjunctive therapy in adults with partial seizures with or without secondary generalisation. *Generalised Anxiety Disorder* For the treatment of Generalised Anxiety Disorder (GAD) in adults. *Peripheral and central neuropathic pain*

Approximately, 70% of all pregabalin prescribing is for neuropathic pain; in Lincolnshire branded prescribing of *Lyrica* increased in response to NHSE advice from 2.2% in 2014/15 to 21% in 2015/16. Despite NHSE guidance, the majority of pregabalin prescribing is still generic; of the new products launched to date only *Rewisca* is beginning to be prescribed. Pregabalin capsules currently appear in category C of the *Drug Tariff* with the reimbursement price set at that of the originator brand, *Lyrica*. This means that virtually all of the pregabalin prescribing in Lincolnshire at present is still being reimbursed at *Lyrica* prices despite the availability of lower cost brands.

Cost Comparison (lower cost products highlighted in **bold**)

	Dose	**Cost (28 Days)**
Pregabalin 75mg capsules (*Alzain*) (Dr Reddy's Laboratories)	**75mg twice daily**	**£45.08**
Pregabalin 75mg capsules (*Lecaent*) , (Actavis UK Ltd)	75mg twice daily	£64.39
Pregabalin 75mg capsules (*Lyrica*) (Pfizer)	75mg twice daily	£64.40
Pregabalin 75mg capsules (*Pregabalin Zentiva*) (Zentiva)	75mg twice daily	£64.40
Pregabalin 75mg capsules (*Rewisca*) (Consilient Health Ltd)	**75mg twice daily**	**£48.30**
Gabapentin 300mg capsules	300mg three times daily	£3.66
Pregabalin 50mg capsules (*Alzain*)	**50mg three times daily**	**£67.62**
Pregabalin 50mg capsules (*Lecaent*)	50mg three times daily	£96.59
Pregabalin 50mg capsules (*Lyrica*)	50mg three times daily	£96.60
Pregabalin 50mg capsules (*Pregabaliin Zentiva)*)	50mg three times daily	£96.60
Pregabalin 50mg capsules (*Rewisca*)	**50mg three times daily**	**£72.45**
Gabapentin 300mg capsules	300mg three times daily	£3.66
Pregabalin 100mg capsules (*Alzain*)	**100mg three times daily**	**£67.62**
Pregabalin 100mg capsules (*Lecaent*)	100mg three times daily	£96.59
Pregabalin 100mg capsules (*Lyrica*)	100mg three times daily	£96.60
Pregabalin 100mg capsules (*Pregabalin Zentiva*)	100mg three times daily	£96.60
Pregabalin 100mg capsules (*Rewisca*)	**100mg three times daily**	**£72.45**
Gabapentin 600mg tablets	600mg three times daily	£9.71
Pregabalin 150mg capsules (*Alzain*)	**150mg twice daily**	**£45.08**
Pregabalin 150mg capsules (*Lecaent*)	150mg twice daily	£64.39
Pregabalin 150mg capsules (*Lyrica*)	150mg twice daily	£64.40
Pregabalin 150mg capsules (*Pregabalin Zentiva*)	150mg twice daily	£64.40
Pregabalin 150mg capsules (*Rewisca*)	**150mg twice daily**	**£48.30**
Gabapentin 600mg tablets	600mg three times daily	£9.71
Pregabalin 200mg capsules (*Alzain*)	**200mg three times daily**	**£67.62**
Pregabalin 200mg capsules (*Lecaent*)	200mg three times daily	£96.59
Pregabalin 200mg capsules (*Lyrica*)	200mg three times daily	£96.60
Pregabalin 200mg capsules (*Pregabalin Zentiva*)	200mg three times daily	£96.60
Pregabalin 200mg capsules (*Rewisca*)	**200mg three times daily**	**£72.45**
Gabapentin 300mg capsules	THREE 300mg (900mg) capsules three times daily	£10.98
Pregabalin 300mg capsules (*Alzain)*	**300mg twice daily**	**£45.08**
Pregabalin 300mg capsules (*Lecaent)*	300mg twice daily	£64.39
Pregabalin 300mg capsules (*Lyrica*)	300mg twice daily	£64.40
Pregabalin 300mg capsules (*Pregabalin Zentiva*)	300mg twice daily	£64.40
Pregabalin 300mg capsules (*Rewisca*)	**300mg twice daily**	**£48.30**
Gabapentin 300mg capsules	THREE 300mg (900mg) capsules three times daily	£10.98

PACEF Recommendations:

(1)When prescribing pregabalin for the treatment of anything other than central or peripheral neuropathic pain, pregabalin should be prescribed as a lower cost brand, specifically as *Alzain* or *Rewisca*. Open generic scripts for pregabalin are still

reimbursed at the higher *Lyrica* price; only branded prescribing of the preferred lower cost products will reduce prescribing costs.
(2)Prescribers should ensure that, as far as reasonably possible, branded *Lyrica* continues to be prescribed by name for all patients requiring pregabalin for the patent protected indication of neuropathic pain (i.e. *Lyrica* 75mg capsules rather than pregabalin 75mg capsules). The *Lyrica* patent is still in contention in the High Court and this guidance is subject to change pending the outcome of this case.
(3)Community pharmacies and dispensing practices should ensure that, as far as reasonably possible, branded *Lyrica* is dispensed against all prescriptions for pregabalin for patients suffering from neuropathic pain. Prescribers are asked to be supportive of community pharmacy requests to change generic prescriptions to branded *Lyrica* for a patent protected indication.
(4)Practices should review all patients currently prescribed pregabalin for neuropathic pain to ensure that, wherever possible, all prescriptions for a patent protected indication specify the *Lyrica* brand.
(5)Pregabalin can continue to be prescribed generically or as a lower cost brand for non-patent protected indications such as: (1) epilepsy; (2) generalised anxiety disorder (GAD) and: (3) pain that cannot be classified as central or peripheral neuropathic pain (unlicensed indication; see definitions below).
(6) Following review *Alzain* and *Rewisca* are the only two lower cost brands approved for use through the *Lincolnshire Joint Formulary*; designation GREEN. In order to achieve the cost saving these products must be prescribed by brand. They should only be prescribed for non-patent protected indications (see table of authorised indications above).
(7) *Lecaent* and *Pregabalin Zentiva* are new higher cost branded formulations of pregabalin priced very similarly to the originator brand *Lyrica*. As a result, both products are not approved for use through the *Lincolnshire Joint Formulary* and are designated RED-RED.
(8) Significant reductions in pregabalin prescribing costs can also be achieved through strength and dose optimisation. For example 150mg twice daily is significantly lower cost than 100mg three times daily.
(8) In the absence of low cost generic pregabalin for neuropathic pain, generic gabapentin provides a potential low cost alternative. Gabapentin is approved for use on the *Lincolnshire Joint Formulary* (designation: GREEN) and is licensed for peripheral neuropathic pain. While upward dose titration is more complex and dosage potentially more frequent, prescribers should consider gabapentin preferentially in new patients requiring treatment with a GABA analogue for neuropathic pain.

RAPID COST COMPARISON: *TRAMADOL 37.5MG/PARACETAMOL 325MG TABLETS AND EFFERVESCENT TABLETS (TRAMACET/TRAMACET EFFERVESCENT)*

A cost comparison reveals the significant difference in cost between the premium price branded tramadol/paracetamol combination product (*Tramacet*) and the components prescribed separately. Prescribers are advised to review all patients on *Tramacet* and *Tramacet Effervescent* with a view to prescribing the paracetamol, and tramadol as separate components wherever possible. As there are no tramadol 37.5mg tablets and paracetamol 325mg tablets available in the UK, prescribers are advised to change people to tramadol 50mg capsules and paracetamol 500mg tablets.

Product	Dose	Cost (28 days)
Tramadol hydrochloride 37.5mg/paracetamol 325mg tablets (*Tramacet*) (Grunenthal)	Maximum daily dose: Two tablets every six hours up to a maximum of eight daily	£36.14 (assuming maximum of eight a day)
Tramadol hydrochloride 37.5mg/paracetamol 325mg	Maximum daily dose: Two tablets every six hours up to a	£34.42 (assuming maximum of eight a day)

tablets (generic)	maximum of eight daily	
Tramadol hydrochloride 37.5mg/paracetamol 325mg effervescent tablets (*Tramacet Effervescent*) (Grunenthal)	Maximum daily dose: Two tablets every six hours up to a maximum of eight daily	£36.14 (assuming maximum of eight a day)
Paracetamol 500mg tablets (generic)	Maximum daily dose: Two tablets every six hours up to a maximum of eight daily	£5.73 (assuming maximum of eight a day)
Tramadol 50mg capsules (generic)	50mg to 100mg every four to six hours	£7.33 (assuming eight a day)

PACEF Recommendation:
Tramadol hydrochloride 37.5mg/paracetamol 325mg tablets (*Tramacet*) and tramadol hydrochloride 37.5mg/paracetamol 325mg effervescent tablets (*Tramacet Effervescent*) are designated RED-RED and should not be prescribed. Neither of these products are approved for use through the *Lincolnshire Joint Formulary.*

TRAMADOL COST COMPARISON

The cost comparison below reveals that prescribing tramadol as generic 50mg capsules is significantly lower cost than any of the once or twice daily modified release preparations such as *Zamadol SR*, *Zydol SR*, *Zamadol 24 hour* and *Zydol XL*.

Product	**Dose**	**Cost (28 days)**
Tramadol 50mg capsules (generic)	50 to 100mg every four to six hours; maximum 400mg daily	£3.66 (assuming 50mg every six hours)* £7.32 (assuming 100mg every six hours)+
Twice daily sustained release		
Tramadol sustained release capsules 50mg (*Zamadol SR*) (Meda)	50mg twice daily	£6.76
Tramadol sustained release capsules 100mg (*Zamadol SR*) (Meda)	100mg twice daily	£13.50*
Tramadol sustained release capsules 150mg (*Zamadol SR*) (Meda)	150mg twice daily	£20.26
Tramadol sustained release capsules 200mg (*Zamadol SR*) (Meda)	200mg twice daily	£27.00+
Tramadol sustained release capsules 50mg (*Zydol SR*) (Grunenthal)	50mg twice daily	£4.29
Tramadol sustained release capsules 100mg (*Zydol SR*) (Grunenthal)	100mg twice daily	£17.04*
Tramadol sustained release capsules 150mg (*Zydol SR*) (Grunenthal)	150mg twice daily	£25.56
Tramadol sustained release capsules 200mg (*Zydol SR*) (Grunenthal)	200mg twice daily	£34.09+
Once daily sustained release		
Tramadol sustained release tablets 150mg (*Zamadol 24 hour*) (Meda)	150mg once daily	£10.70
Tramadol sustained release tablets 200mg (*Zamadol 24 hour*) (Meda)	200mg once daily	£14.26*
Tramadol sustained release tablets 300mg (*Zamadol 24 hour*) (Meda)	300mg once daily	£21.39
Tramadol sustained release tablets 400mg (*Zamadol 24 hour*) (Meda)	400mg once daily	£28.51+
Tramadol sustained release tablets 150mg (*Zydol XL*) (Grunenthal)	150mg once daily	£11.37
Tramadol sustained release tablets 200mg (*Zydol XL*) (Grunenthal)	200mg once daily	£16.78*
Tramadol sustained release tablets 300mg (*Zydol XL*) (Grunenthal)	300mg once daily	£23.28
Tramadol sustained release tablets 400mg (*Zydol XL*) (Grunenthal)	400mg once daily	£30.31+

*comparable doses
+ comparable doses.

MEDICINES AND HEALTHCARE REGULATORY AGENCY: *DRUG SAFETY UPDATE* (APRIL 2016)

SGLT2 INHIBITORS: UPDATED ADVICE ON THE RISK OF DIABETIC KETOACIDOSIS

The MHRA have highlighted again the risk of diabetic ketoacidosis in patients taking the SGLT2 inhibitors, canagliflozin, dapagliflozin and empagliflozin.

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are licensed for use in adults with type 2 diabetes to improve glycaemic control. Serious, life-threatening, and fatal cases of diabetic ketoacidosis (DKA) have been reported in patients taking a SGLT2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin).

The European Medicines Agency have previously conducted a review of the association of DKA with SGLT2 inhibitor use and have concluded that this side effect is rare (affecting between 1 in 1000 and 1 in 10,000 patients). The results of this review were communicated to all prescribers in the June 2015 edition of the MHRA *Drug Safety Update* and guidance was issued in *PACE Bulletin* Vol 9 No 12 (July 2015)

Up to 26 February 2016, the MHRA had received 118 Yellow Card reports of DKA and associated reactions in patients taking an SGLT2 inhibitor in the UK. In several cases, blood glucose levels were only moderately elevated (e.g. <14 mmol/L) — representing an atypical presentation for DKA, which could delay diagnosis and treatment. The MHRA therefore stress the importance of informing patients of the signs and symptoms of DKA (e.g. rapid weight loss, feeling sick or being sick, stomach pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat) and test for raised ketones in patients with these signs and symptoms.

A substantial proportion of the cases reported concerned off-label use in patients with type 1 diabetes. SGLT2 inhibitors are only licensed for use in patient with type 2 diabetes and should not be used in patients with type 1 diabetes. Many of the cases of DKA occurred during the first 2 months of treatment and some shortly after stopping the SGLT2 inhibitor. In some cases, just before or at the first development of DKA, patients had dehydration, low food intake, weight loss, infection, surgery, vomiting, a decrease in insulin dose, or poor control of diabetes.

Risk factors

The mechanism by which SGLT2 inhibitors might lead to DKA has not been established. However, the following factors may predispose patients taking an SGLT2 inhibitor to DKA:

- a low beta cell function reserve (e.g. patients with type 2 diabetes who have low C-peptide levels, latent autoimmune diabetes in adults [LADA], or a history of pancreatitis).
- conditions leading to restricted food intake or severe dehydration.
- sudden reduction in insulin.
- increased insulin requirements due to acute illness.
- surgery.
- alcohol abuse.

Advice for healthcare professionals

When treating patients who are taking a SGLT2 inhibitor (canagliflozin, dapagliflozin, or empagliflozin):

- Inform them of the signs and symptoms of diabetic ketoacidosis (DKA) – see above – and advise them to seek immediate medical advice if they develop any of these.

- Test for raised ketones in patients with ketoacidosis symptoms, even if plasma glucose levels are near-normal.
- Discuss the risk factors for DKA with patients and use a SGLT2 inhibitor with caution in patients who have risk factors.
- Discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed.
- Do not restart treatment with any SGLT2 inhibitor in patients who experienced DKA during use unless another cause for DKA was identified and resolved.
- Interrupt treatment with the SGLT2 inhibitor in patients who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the patient's condition has stabilised.
- report suspected side effects to SGLT2 inhibitors or any other medicines on a Yellow Card.

APOMORPHINE WITH DOMPERIDONE: MINIMISING RISK OF CARDIAC SIDE EFFECTS

Apomorphine and domperidone prescribed concurrently carries an increased risk of QT prolongation and associated serious cardiac side effects.

Apomorphine injection (*APO-go*) is a dopamine agonist used to treat refractory motor fluctuations in people with Parkinson's disease. Domperidone (*Motilium*) is usually started at least two days before apomorphine to control the expected side effects of nausea and vomiting.

Domperidone and the risk of cardiac side effects

In 2014, a review by EU medicines regulators concluded that domperidone is associated with a small increased risk of QT-interval prolongation, serious ventricular arrhythmias, and sudden cardiac death. A higher risk was observed in people older than 60 years, people taking daily oral doses of more than 30 mg, and in those taking other QT-prolonging medicines or cytochrome P450 3A4 inhibitors at the same time as domperidone. As a result of this review, the licensed indication for domperidone was restricted to relief of nausea and vomiting, the licensed dose was reduced, and several contraindications were introduced. This information was published in May 2014 *Drug Safety Update* and formed the basis of local advice published in *PACE Bulletin* Vol 8 No 12 (June 2014).

Apomorphine with domperidone and the risk of QT-prolongation

Apomorphine can increase the risk of QT-prolongation at high doses.
A review by EU medicines regulators of the safety of concomitant apomorphine and domperidone use has recently finished. This review concluded that the risk of QT-prolongation may be increased in people on concomitant apomorphine and domperidone who have certain risk factors, including:

- pre-existing QT-interval prolongation.
- serious underlying cardiac disorders such as heart failure.
- severe hepatic dysfunction.
- significant electrolyte disturbances.
- concomitant drug therapy that may increase domperidone levels (e.g. cytochrome P450 3A4 inhibitors).

Patients receiving apomorphine and domperidone require an assessment of cardiac risk factors and ECG monitoring to reduce the risk of serious arrhythmia related to QT-prolongation.

Advice for healthcare professionals:

- Before starting treatment, carefully consider whether the benefits of concomitant apomorphine and domperidone treatment outweigh the small increased risk of cardiac side effects.
- Discuss the benefits and risks of apomorphine with patients and carers and advise them to contact their doctor immediately if they develop palpitations or syncopal symptoms during treatment.
- Check the QT-interval before starting domperidone, during the apomorphine initiation phase and if clinically indicated thereafter (e.g. if a QT-prolonging or interacting drug is started or if symptoms of cardiac side effects are reported).
- Regularly review domperidone treatment to ensure patients take the lowest effective dose for the shortest duration.
- Advise patients to inform their doctor of any changes that could increase their risk of arrhythmia, such as:
    - symptoms of cardiac or hepatic disorders.
    - conditions that could cause electrolyte disturbances (eg, gastroenteritis or starting a diuretic).
    - starting any other medicines.
- Please continue to report suspected side effects to apomorphine, domperidone, or any other medicine on a Yellow Card.

PACEF Comment

Updated MHRA advice on concomitant use of apomorphine and domperidone is consistent with PACEF advice as it advises careful consideration of the risks and benefits of combination treatment, the need to involve the patient and or carer in the decision making process and the necessity to continue to review treatment to ensure that the lowest dose is used for the shortest period. Management of patients who continue to suffer nausea and vomiting associated with apomorphine therapy will need to be discussed with the responsible consultant and consideration given to the risks and benefits of continuation of apomorphine treatment. Apomorphine injection (*APO-go*) is designated AMBER with shared care on the *Lincolnshire Joint Formulary*; it should only be prescribed in accordance with formal shared care arrangements agreed with specialist centres.

LIVE ATTENUATED VACCINES: AVOID USE IN THOSE WHO ARE CLINICALLY IMMUNOSUPPRESSED

Healthcare professionals working in primary and secondary care should ensure that clinically significant immunosuppression in a patient is identified before administration of a live attenuated vaccine.

Background
Some recommended vaccines contain live, attenuated organisms, which work by mimicking a natural infection. Live attenuated vaccines should not be given to people who are clinically immunosuppressed (either due to drug treatment or underlying illness) because the vaccine strain could replicate too much and cause an extensive, serious infection. A minor immunodeficiency may not necessarily contraindicate vaccination, and the Summary of Product Characteristics for a particular vaccine will explain specific contraindications and warnings. The Green Book *Immunisation against infectious disease* should also be consulted.

Fatal BCG infection in neonates after in utero exposure to TNFα antagonist
The MHRA have received 4 Yellow Card reports regarding neonates who have died from disseminated BCG or tuberculosis infection after exposure to a TNFα antagonist in utero; they were probably not known to be immunosuppressed at the time of vaccination.
As a precaution, any infant who has been exposed to immunosuppressive treatment from the mother either in utero during pregnancy or via breastfeeding should have any live attenuated vaccination deferred for as long as a postnatal influence on the immune status of the infant remains possible. In the case of in utero exposure to TNFα antagonists and other biological medicines, this period should be until the infant is age 6 months, after which time vaccination should be considered.

Shingles vaccination in elderly patients with immunosuppression
The MHRA have received Yellow Cards reporting that several elderly patients have received shingles vaccine (*Zostavax*) at a time when they were possibly immunosuppressed (e.g. due to treatment for a transplant or due to lymphoproliferative disorders). The suspected adverse reactions reported in these Yellow Cards are possibly a consequence of a disseminated viral infection caused by the vaccine strain. It is important for all healthcare professionals to be familiar with the contraindications and special precautions associated with the shingles vaccine before proceeding with immunisation.

Reminder regarding close contacts of immunosuppressed individuals
Public Health England advise that to minimise the risk of infection in immunosuppressed individuals for whom live vaccines are contraindicated, their close contacts should be fully immunised according to the UK schedule, as a matter of priority. Close contacts of severely immunosuppressed individuals should also be offered vaccination against varicella and influenza. This will reduce the risk of exposure of vulnerable individuals to the serious consequences of vaccine-preventable infections.

Reminder for healthcare professionals:

- Live attenuated vaccines should not routinely be given to people who are clinically immunosuppressed (either due to drug treatment or underlying illness).
- It is important for healthcare professionals who are administering a particular vaccine to be familiar with the contraindications and special precautions before proceeding with immunisation.
- Specialists with responsibility for an immunosuppressed patient who may be in a group eligible for a live attenuated vaccine should include in their correspondence with primary care a statement of their opinion on the patient's suitability for the vaccine.
- If primary care professionals are in any doubt as to whether a person due to receive a live attenuated vaccine may be immunosuppressed at the time, immunisation should be deferred until secondary care specialist advice has been sought, including advice from an immunologist if required.

- Remember that close contacts of immunosuppressed individuals should be fully immunised to minimise the risk of infection of vaccine-preventable diseases in immunosuppressed individuals.

MEPROBAMATE: LICENCE TO BE CANCELLED

Meprobamate 400mg tablets are due to be withdrawn at the end of the year.

Following an EU wide review of meprobamate, the remaining licence holder in the UK has ceased manufacturing and the licence will be cancelled by the end of 2016.

Advice for healthcare professionals:

- Prescribers should review the treatment of any patient who is currently receiving a meprobamate-containing medicine with a view to switching them to an alternative treatment
- Prescribers should not start any new patients on medicines that contain meprobamate

Background

Meprobamate is a carbamate used for short-term treatment of anxiety states or musculoskeletal disorders where, in either case, there is muscle tension or painful muscle spasm. In 2012, the European Medicines Agency recommended withdrawal of meprobromate-containing medicines from the market following a review of their safety and effectiveness. The review concluded that the benefits of meprobamate do not outweigh its risks (which include dependence, withdrawal reactions, and abuse).

Withdrawal of licence

No new stock will be released into the normal distribution chain after 31 December 2016, although existing stock placed on the market (and therefore already in the supply chain) before that date is likely to be dispensed until the products approach their expiry date. Since 2012, prescribing of meprobamate in the UK has decreased; however, a small number of patients continue to receive it. These patients should be reviewed and where possible switched to an alternative safer treatment.

PACEF Comment

Meprobamate 400mg tablets are not available through the *Lincolnshire Joint Formulary* and are designated RED-RED. Nonetheless, a small number of prescriptions are issued within all four Lincolnshire CCGs each year. Prescribers are advised to review all patients currently taking meprobamate as the drug is due to be discontinued at the end of 2016.

PARAFFIN-BASED SKIN EMOLLIENTS ON DRESSINGS OR CLOTHING: FIRE RISK

Smoking or a naked flame could cause patients' dressings or clothing to catch fire when being treated with a paraffin-based emollient that is in contact with their dressing or clothing.

Reminder for healthcare professionals:

- Advise patients not to: smoke; use naked flames (or be near people who are smoking or using naked flames); or go near anything that may cause a fire while emollients are in contact with their medical dressings or clothing.
- Change patient clothing and bedding regularly—preferably daily—because emollients soak into fabric and can become a fire hazard.

- Incidents should be reported to NHS England's Serious Incident Framework.

Examples of paraffin-based emollients include:
- white soft paraffin
- white soft paraffin plus 50% liquid paraffin
- emulsifying ointment

The risk is greater when these preparations are applied to large areas of the body, or when dressings or clothing become soaked with emollient.

The MHRA are aware of a recent fatal incident reported to the NHS England National Reporting and Learning System, in which a naked flame ignited emollient in contact with a patient's dressings and clothing.

PACEF Comment
The potential increased fire risk associated with the use of paraffin containing emollients was discussed at the February 2016 meeting of PACEF in response to a local incident related to a fatal fire involving a patient receiving home oxygen therapy. Further non-fatal incidents involving inadvertent ignition of paraffin based emollients have also occurred in county. PACEF reviewed the emollients section of the *Lincolnshire Joint Formulary* recommending that no or low paraffin content products are preferable in high risk groups; advice was published in *PACE Bulletin* Vol 10 No 5 (March 2016). PACEF have also approved *Eumocream* a glycerol based emollient for inclusion on the *Lincolnshire Joint Formulary* as an alternative when a paraffin-free product is indicated.

EUROPEAN MEDICINES AGENCY, REVIEW OF CANAGLIFLOZIN (APRIL 2016)

The European Medicines Agency has started a review of canagliflozin after an increase in amputations, mostly toes, was observed in an ongoing clinical trial called CANVAS. The CANagliflozin cardiovascular Assessment Study (CANVAS) is a long-term cardiovascular outcomes study designed to compare canagliflozin plus standard care with placebo plus standard care in patients with diabetes at risk of cardiovascular disease. At this stage in the trial, there are cases of lower limb amputation in both the canagliflozin and the placebo groups, although the incidence is higher in the canagliflozin groups. Another study known as CANVAS-R is showing similar trends. No increase in such amputations has been seen in 12 other completed canagliflozin trials. This is an ongoing EMA review and no conclusion has yet been reached.

PACEF Comment:
All patients with diabetes, particularly those who are poorly controlled or with pre-existing heart or circulatory disease, are at increased risk of infection and ulceration that can lead to lower limb amputation. Healthcare professionals should ensure that diabetic patients are aware of the importance of routine foot care to avoid cuts or sores of the feet and to treat them promptly should they occur to prevent infection and ulceration. Patients at increased risk of amputation (such as those who have already had a previous amputation) should be carefully monitored. Doctors may consider stopping canagliflozin in patients who develop significant foot problems.

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