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 13 **August 2016**

What's new this month?

- **Doxycycline 40mg modified release capsules (*Efracea*) for the treatment of facial rosacea have been re-assessed and continue to be designated RED-RED (see page 3).**
- **Brivaracetam tablets and 10mg/ml oral solution (*Briviact*) are designated RED-RED and not approved for inclusion in the *Lincolnshire Joint Formulary*; specialist requests for this drug to be initiated or prescribed in primary care for treatment resistant patients with partial onset seizures will need to be considered through the Individual Funding Request process (see page 5).**
- **Levetiracetam tablets and oral solution 100mg/ml are available through the *Lincolnshire Joint Formulary*, designation AMBER without shared care. MHRA advice on switching antiepileptic drugs published in November 2013 identifies levetiracetam as a Category 3 antiepileptic drug; this means that there is no data to suggest that switching from higher cost brands (such as *Keppra*) to lower cost generics presents a problem. All new patients on levetiracetam should receive the lower cost generic product; existing patients on *Keppra* should be considered for switch to generic. Lincolnshire data suggests that over 85% of levetiracetam prescribing is generic (see page 5).**
- **Diltiazem 60mg modified release tablets (*Retalzem*) are prohibitively expensive in comparison to the *Tildiem* brand and should not be prescribed; they are designated RED-RED and not included in the *Lincolnshire Joint Formulary*. Prescribers should ensure that all prescriptions for diltiazem 60mg modified release tablets are prescribed as *Tildiem*. Prescribers are encouraged to review their prescribing to ensure that all diltiazem prescribing is by brand. Where a modified or sustained release product is required, once daily products are preferred, specifically the two lowest cost once daily brands, *Angitil XL*, *Viazem XL* and *Zemtard XL* (see page 6).**
- **Naproxen effervescent tablets 250mg (*Stirlescent*) are significantly higher in cost than naproxen tablets or gastro-resistant tablets, but lower in cost than the unlicensed liquid special, naproxen 125mg in 5ml oral suspension. Ibuprofen oral suspension 100mg in 5ml is available on the *Lincolnshire Joint Formulary* and presents a preferred alternative at an equivalent cost. In view of this, naproxen effervescent tablets 250mg (*Stirlescent*) are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary*. Naproxen 125mg in 5ml oral suspension (unlicensed special) is also designated RED-RED (see page 9).**
- **The MHRA 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 should consider stopping canagliflozin in patients who develop significant foot problems (see page 10).**

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SUMMARY OF PACEF DECISIONS: *JULY 2016 UPDATE*

Device, Dressing or Drug	**Indication(s)**	**Traffic Light and *Joint Formulary* Status**
Brivaracetam 10mg, 25mg, 50mg, 75mg and 100mg tablets and 10mg/ml oral solution (*Briviact*) (UCB)	For use as an adjunct in partial-onset seizures with or without secondary generalisation.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*. Individual Funding Requests will be considered in exceptional cases.
Diltiazem 60mg modified release tablets (*Retalzem*) (Kent Pharmaceuticals)	Prophylaxis and treatment of angina pectoris	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*. All prescriptions for diltiazem 60mg modified release tablets should specify the lower cost *Tildiem* brand.
Diltiazem 60mg modified release tablets (*Tildiem*) (Sanofi-Aventis)	Prophylaxis and treatment of angina pectoris	GREEN Included in the *Lincolnshire Joint Formulary*. All prescriptions for diltiazem 60mg modified release tablets should specify the lower cost *Tildiem* brand.
Diltiazem 120mg, 180mg, 240mg, 300mg and 360mg SR capsules (*Viazem XL*) (Genus)	For angina and mild to moderate hypertension	GREEN Included in the *Lincolnshire Joint Formulary*. Where a once daily SR diltiazem preparation is indicated either *Viazem XL* or *Zemtard* should be preferred. All prescribing should be brand specific.
Diltiazem 120mg, 180mg, 240mg and 300mg SR capsules (*Zemtard XL*) (Galen)	For angina and mild to moderate hypertension	GREEN Included in the *Lincolnshire Joint Formulary*. Where a once daily SR diltiazem preparation is indicated either *Viazem XL* or *Zemtard XL* should be preferred. All prescribing should be brand specific.
Doxycycline 40mg modified release capsules (MR) (*Efracea*) (Galderma)	For the treatment of facial rosacea.	RED-RED. Not approved for inclusion in the *Lincolnshire Joint Formulary*.
Levetiracetam tablets 250mg, 500mg, 750mg, 1g and oral solution 100mg/ml (generic)	For monotherapy in partial seizures with or without secondary generalisation in patients with newly diagnosed epilepsy. Adjunct in partial seizures with or without secondary generalisation. Adjunct in juvenile myoclonic epilepsy. Adjunct in idiopathic generalised epilepsy.	AMBER without shared care. Included in the *Lincolnshire Joint Formulary.*
Naproxen effervescent tablets 250mg (Stirlescent) (Stirling Health)	For the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, acute musculoskeletal disorders and	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*. Ibuprofen oral suspension 100mg in 5ml is available on the

	dysmenorrhoea.	*Lincolnshire Joint Formulary* and presents a preferred alternative at an equivalent cost.
Naproxen 125mg in 5ml oral suspension (Tariff special)	Unlicensed	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*. Ibuprofen oral suspension 100mg in 5ml is available on the *Lincolnshire Joint Formulary* and presents a preferred alternative at a much lower cost.

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

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

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

REVIEW: *DOXYCYCLINE 40MG MODIFIED RELEASE CAPSULES (EFRACEA)*

This article is an updated version of a New Drug Assessment that was originally published in *PACE Bulletin* Vol 4 No 9 (June 2010) and updated in *PACE Bulletin* Vol 7 No 2 (January 2013). Updated and new text is in italics.

After a review of new evidence, doxycycline 40mg modified release (MR) capsules (*Efracea*) continue to be designated RED-RED.

Doxycycline 40mg modified release (MR) (*Efracea*) is the first doxycycline formulation with a marketing authorisation for the treatment of adult patients with facial rosacea. Whilst doxycycline has been a recognised treatment for this condition for some time, none of the previously existing preparations are licensed for this purpose. Conventionally, doxycycline 100mg daily has been prescribed for moderately severe acne (*unlicensed use*). Doxycycline 40mg MR capsules (*Efracea*) contain a sub-antimicrobial dose of doxycycline which, nonetheless, appears to have anti-inflammatory properties. As the dose of doxycycline used is below that required for its antimicrobial effect, chronic use should not be associated with increasing risk of intestinal bacterial resistance.

Clinical evidence from two 16 week placebo controlled randomized controlled trials (RCTs) demonstrates a reduction in the number of lesions with active treatment and no effect on other symptoms such as the incidence of nodules and the extent and severity of erythema. *Efracea* emerges from these trials with evidence of superiority over placebo.

A Cochrane review in 2011 looked at a range of effective and evidence-based management strategies for rosacea. 58 RCTs were identified covering a range of different therapies including topical metronidazole, oral antibiotics, topical azelaic cream or gel, topical benzoyl peroxide and/or combined with topical antibiotics, sulphacetamide/sulphur and others. The majority of the trials identified were assessed as being at high or unclear risk of bias. However, there was some evidence to support the effectiveness of topical metronidazole, azelaic acid and doxycycline 40mg in the treatment of moderate to severe rosacea. There was no statistically significant difference in effectiveness between doxycycline 40mg and 100mg but there were fewer adverse effects associated with the 40mg strength.

The ORCA (Oracea for Rosacea) trial was a company-sponsored open-label, community-based, 12-week assessment of the effectiveness and safety of doxycycline 40mg MR in patients who would otherwise have been treated with antibiotic-dose doxycycline. 1196 patients took doxycycline 40mg MR daily for 12 weeks and investigators evaluated each patient's rosacea severity and erythema at baseline and at weeks 2, 4, 8 and 12. The primary outcome measure was the change in investigator global assessment score of rosacea severity from baseline to end point (week 12). By the end of the study, 35.5% of participants had clear and 39.1% had near clear scores. *At this stage, direct comparative data with doxycycline 100mg was still lacking.*

In July 2016, PACEF reviewed a small study comparing doxycycline 40mg MR with doxycycline 100mg in 91 adult patients with moderate to severe rosacea. All patients were using metronidazole 1% gel and were randomized to receive one of the doxycycline preparations. In terms of change in total lesion count, both products were found to be equally effective with fewer reports of adverse effects in the doxycycline 40mg MR group.

PACEF also reviewed two small scale studies looking at the effect of doxycycline 20mg MR on antimicrobial resistance. These studies detected no antimicrobial effect on the skin, faecal and vaginal flora and no evidence of an increased number or severity of resistant organisms emerging with doxycycline 20mg MR. Unfortunately, neither of these studies provides confirmation of claims that doxycycline 40mg MR is associated with a lower incidence or decreased likelihood of emerging bacterial resistance to doxycycline. In addition, comparative evidence is lacking around the risk of emerging resistance with doxycycline 100mg.

A cost comparison of doxycycline 40mg modified release (*Efracea*) with other alternative treatments reveals the following:

	Dose	*Cost (28 days)*
Doxycycline 40mg modified release capsules (MR) (Efracea) (Galderma)	*40mg once daily*	*£15.98*
Doxycycline 100mg capsules (generic) (unlicensed)	*100mg once daily*	*£3.01*
Lymecycline 408mg capsules (Tetralysal) (Galderma)	*408mg once daily*	*£6.65*
Oxytetracycline 250mg tablets (generic)	*500mg twice daily*	*£3.60*
Tetracycline 250mg tablets (generic)	*500mg twice daily*	*£7.92*

PACEF Recommendation:

New comparative evidence suggests that doxycycline 40mg modified release capsules (Efracea) are as effective as doxycycline 100mg and better tolerated in the treatment of facial rosacea. However, such evidence is limited and of poor quality. In addition, while limited evidence exists supporting claims that doxycycline 20mg MR is not linked to the emergence of doxycycline resistant organisms, evidence supporting similar claims around doxycycline 40mg MR is still lacking. In the absence of conclusive evidence to support such claims, PACEF remain unconvinced that any additional benefits are commensurate with the increased cost. As a result of this, doxycycline 40mg modified release capsules (Efracea) remain RED-RED and are still not approved for use through the Lincolnshire Joint Formulary.

NEW DRUG ASSESSMENT: *BRIVARACETAM TABLETS AND 10MG/ML ORAL SOLUTION (BRIVIACT)*

Brivaracetam tablets and 10mg/ml oral solution (*Briviact*) are designated RED-RED and not approved for inclusion in the *Lincolnshire Joint Formulary*; specialist requests for this drug to be initiated or prescribed in primary care for treatment resistant patients with partial onset seizures will need to be considered through the Individual Funding Request process.

Brivaracetam tablets and 10mg/ml oral solution (*Briviact*) are indicated for use in adults and adolescents as adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalisation. Brivaracetam has a similar chemical structure and mechanism of action to levetiracetam, but with higher affinity binding to synaptic vesicle protein 2A (SV2A).

A meta-analysis of six trials involving 2,399 patients with drug resistant focal epilepsy uncontrolled by one or more concomitant anti-epileptic drugs, demonstrated that add-on brivaracetam was more effective than placebo in reducing seizure frequency. There was a possible reduced effect in patients who had previously been exposed to levetiracetam. There are no head to head trials comparing brivaracetam with levetiracetam or any other anti-epileptics. Brivaracetam should not be taken with levetiracetam.

The most frequently reported adverse events were irritability, insomnia, depression and anxiety (2-3% of patients); aggression, agitation, and memory impairment were also reported, but to a lesser extent.

A cost comparison with levetiracetam products reveals that brivaracetam is significantly more expensive than generic levetiracetam, but comparably priced with the levetiracetam originator brand, *Keppra.* Both *Briviact* and *Keppra* are premium priced branded anti-epileptic drugs and are significantly more expensive than established first and second line agents such as carbamazepine, clobazam, gabapentin, lamotrigine, sodium valproate and topiramate.

Drug	Dose	Cost (28 days)	Cost per patient per year
Brivaracetam tablets (*Briviact*) (UCB)	25mg to 100mg twice daily	£129.64	£1,689.95
Brivaracetam 10mg/ml oral solution (*Briviact*) (UCB)	25mg (2.5ml) to 100mg (10ml) twice daily	£54.05 to £108.11	£702.65 to £1,405.43
Levetiracetam tablets (generic)	250mg to 1.5g twice daily	£2.70 to £10.90	£35.20 to £142.09
Levetiracetam tablets (*Keppra*) (UCB)	250mg to 1.5g twice daily	£26.14 to £156.84	£340.75 to £2,044.52
Levetiracetam tablets (*Desitrend*) (Desitin)	250mg to 1.5g twice daily	£20.91 to £108.01	£271.83 to £1,404.19
Levetiracetam oral	250mg (2.5ml) to 1.5g	£3.83 to £22.96	£49.79 to £298.48

solution 100mg/ml (generic)	(15ml) twice daily		
Levetiracetam oral solution 100mg/ml (*Keppra*) (UCB)	250mg (2.5ml) to 1.5g (15ml) twice daily	£31.25 to £187.46	£406.25 to £2,436.98

PACEF Recommendation

Brivaracetam (*Briviact*) is a high cost, second or third line anticonvulsant chemically similar and with a similar mechanism of action to levetiracetam. A meta-analysis of six trials confirms that brivaracetam is more effective at reducing seizure frequency than placebo in patients with drug resistant focal epilepsy uncontrolled by one or more concomitant anti-epileptic drugs. At present, there is no comparative evidence against levetiracetam or any other anti-epileptic drug. In addition, brivaracetam is significantly more expensive than generic levetiracetam and many other first and second line antiepileptic drugs. A cost comparison reveals that it is comparably priced to the originator brand of levetiracetam (*Keppra*). In view of these concerns, brivaracetam 10mg, 25mg, 50mg, 75mg and 100mg tablets and 10mg/ml oral solution (*Briviact*) are designated RED-RED and not approved for inclusion in the *Lincolnshire Joint Formulary*; specialist requests for this drug to be initiated or prescribed in primary care for treatment resistant patients with partial onset seizures will need to be considered through the Individual Funding Request process. Levetiracetam tablets and oral solution 100mg/ml are approved for use through the *Lincolnshire Joint Formulary*, designation AMBER without shared care. MHRA advice on switching antiepileptic drugs published in November 2013 identifies levetiracetam as a Category 3 antiepileptic drug; this means that there is no data to suggest that switching from higher cost brands (such as *Keppra*) to lower cost generics presents a problem. All new patients on levetiracetam should receive the lower cost generic product; existing patients on *Keppra* should be considered for switch to generic (see *PACE Bulletin* Vol 8 No 5 (March 2014)). Lincolnshire data suggests that over 85% of levetiracetam prescribing is already generic.

RAPID COST COMPARISON: *DILTIAZEM 60MG MODIFIED RELEASE TABLETS (RETALZEM)*

***Retalzem* is a new tablet formulation of diltiazem 60mg. The means of formulation of thrice daily diltiazem 60mg tablets means that they are designated as modified release in the *BNF.* A cost comparison with alternatives reveals that *Retalzem* and generic diltiazem 60mg modified release tablets are both prohibitively expensive in comparison to the *Tildiem* brand.**

Product	Dose	Cost (28 days)
Diltiazem 60mg modified release tablets (generic)	60mg three times daily	£41.60
Diltiazem 60mg modified release tablets (*Retalzem*) (Kent Pharmaceuticals)	60mg three times daily	£41.28
Diltiazem 60mg modified release tablets (*Tildiem*) (Sanofi)	**60mg three times daily**	**£7.43**

Lowest cost product in bold

PACEF Recommendation

Diltiazem 60mg modified release tablets (*Reltazem*) are prohibitively expensive in comparison to the *Tildiem* brand and should not be prescribed; they are designated RED-RED and not included in the *Lincolnshire Joint Formulary*. Prescribers should

ensure that all prescriptions for diltiazem 60mg modified release tablets are prescribed by brand as *Tildiem*.

REVIEW: *LONGER-ACTING DILTIAZEM FORMULATIONS*

Prescribers are encouraged to review their diltiazem prescribing to ensure that all diltiazem prescribing is by brand name. Where a modified or sustained release product is required once daily products are preferred, specifically the two lowest cost once daily brands, *Viazem XL* and *Zemtard XL*.

Twice daily products

Diltiazem 90mg MR capsules (*Adizem SR*) (Napp)	90mg twice daily	£8.50
Diltiazem 120mg MR capsules (*Adizem SR*) (Napp)	120mg twice daily	£9.45
Diltiazem 120mg MR tablets (*Adizem SR*) (Napp)	120mg twice daily	£14.72
Diltiazem 180mg MR capsules (*Adizem SR*) (Napp)	180mg twice daily	£14.15
Diltiazem 90mg MR capsules (*Angitil SR*) (Chiesi)	**90mg twice daily**	**£7.03**
Diltiazem 120mg MR capsules (*Angitil SR*) (Chiesi)	**120mg twice daily**	**£6.91**
Diltiazem 180mg MR capsules (*Angitil SR*) (Chiesi)	**180mg twice daily**	**£13.27**
Diltiazem 60mg MR capsules (*Dilcardia SR*) (Generics)	60mg twice daily	£6.03
Diltiazem 90mg MR capsules (*Dilcardia SR*) (Generics)	90mg twice daily	£9.61
Diltiazem 120mg MR capsules (*Dilcardia SR*) (Generics)	120mg twice daily	£10.69
Diltiazem 60mg MR capsules (*Dilzem SR*) (Teva UK)	60mg twice daily	£6.04
Diltiazem 90mg MR capsules (*Dilzem SR*) (Teva UK)	90mg twice daily	£11.29
Diltiazem 120mg MR capsules (*Dilzem SR*) (Teva UK)	120mg twice daily	£12.89
Diltiazem 90mg SR tablets (*Tildiem Retard*) (Sanofi-Aventis)	**90mg twice daily**	**£7.27**
Diltiazem 120mg SR tablets (*Tildiem Retard*) (Sanofi-Aventis)	**120mg twice daily**	**£7.15**

Lower cost products in bold

Once daily products

Diltiazem 120mg SR capsules (*Adizem XL*) (Napp)	120mg once daily	£9.14
Diltiazem 180mg SR capsules (*Adizem XL*) (Napp)	180mg once daily	£10.37
Diltiazem 200mg SR capsules (*Adizem XL*) (Napp)	200mg once daily	£6.30
Diltiazem 240mg SR capsules (*Adizem XL*) (Napp)	240mg once daily	£11.52
Diltiazem 300mg SR capsules	300mg once daily	£9.14

(*Adizem XL*) (Napp)		
Diltiazem 240mg SR capsules (*Angitil XL*) (Chiesi)	**240mg once daily**	**£7.94**
Diltiazem 300mg SR capsules (*Angitil XL*) (Chiesi)	**300mg once daily**	**£6.98**
Diltiazem 120mg SR capsules (*Dilzem XL*) (Teva UK)	120mg once daily	£7.78
Diltiazem 180mg SR capsules (*Dilzem XL*) (Teva UK)	180mg once daily	£11.55
Diltiazem 240mg SR capsules (*Dilzem XL*) (Teva UK)	240mg once daily	£11.03
Diltiazem 120mg SR capsules (*Slozem XL*) (Merck Serono)	120mg once daily	£7.00
Diltiazem 180mg SR capsules (*Slozem XL*) (Merck Serono)	180mg once daily	£7.80
Diltiazem 240mg SR capsules (*Slozem XL*) (Merck Serono)	240mg once daily	£8.20
Diltiazem 300mg SR capsules (*Slozem XL*) (Merck Serono)	300mg once daily	£8.50
Diltiazem 200mg SR capsules (*Tildiem LA*) (Sanofi)	200mg once daily	£6.29
Diltiazem 300mg SR capsules (*Tildiem LA*) (Sanofi)	300mg once daily	£9.01
Diltiazem 120mg SR capsules (*Viazem XL*) (Genus)	**120mg once daily**	**£6.60**
Diltiazem 180mg SR capsules (*Viazem XL*) (Genus)	**180mg once daily**	**£7.36**
Diltiazem 240mg SR capsules (*Viazem XL*) (Genus)	**240mg once daily**	**£7.74**
Diltiazem 300mg SR capsules (*Viazem XL*) (Genus)	**300mg once daily**	**£8.03**
Diltiazem 360mg SR capsules (*Viazem XL*) (Genus)	**360mg once daily**	**£13.85**
Diltiazem 120mg SR capsules (*Zemtard XL*) (Galen)	**120mg once daily**	**£5.19**
Diltiazem 180mg SR capsules (*Zemtard X*L) (Galen)	**180mg once daily**	**£5.27**
Diltiazem 240mg SR capsules (*Zemtard XL*) (Galen)	**240mg once daily**	**£5.36**
Diltiazem 300mg SR capsules (*Zemtard XL*) (Galen)	**300mg once daily**	**£5.70**

Lower cost products in bold

PACEF Recommendations

- **Standard *BNF* advice is that all longer-acting formulations of diltiazem should be prescribed by brand name as there may be a variation in clinical effect between different brands of the same strength. Specific brand name prescribing can also help to avoid confusion between once daily and twice daily formulations. A recent review of prescribing of diltiazem in Lincolnshire reveals that most prescribing is by brand, although there is a small but significant legacy of generic prescribing in need of review. Individual CCG figures are as follows:**

CCG	Percentage of all diltiazem preparations prescribed by brand name (Items)

LECCG	78.3%
LWCCG	85%
SLCCG	82.2%
SWLCCG	87.2%

- **In general, once daily sustained release preparations are lower cost than twice daily modified release formulations and should be preferred. Current *Formulary* guidance supports the first line use of the two lowest cost once daily brands, *Viazem XL* and *Zemtard XL* (see cost comparison above).**
- **Scrutiny of prescribing figures shows that higher cost products like *Adizem XL* and *Adizem SR* are still widely prescribed.**
- **Prescribers are encouraged to review their diltiazem prescribing to ensure that (1) a brand name product is always specified and (2) a lower cost once daily preparation is usually preferred.**

RAPID COST COMPARISON: *NAPROXEN 250MG EFFERVESCENT TABLETS (STIRLESCENT)*

Naproxen effervescent tablets 250mg (*Stirlescent*) are significantly higher in cost than naproxen tablets or gastro-resistant tablets, but lower in cost than the unlicensed liquid special, naproxen 125mg in 5ml oral suspension. Ibuprofen oral suspension 100mg in 5ml is available on the *Lincolnshire Joint Formulary* and presents a preferred alternative at an equivalent cost. In view of this, naproxen effervescent tablets 250mg (*Stirlescent*) are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary.*

Naproxen 250mg effervescent tablets (*Stirlescent*) have recently been licensed for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, acute musculoskeletal disorders and dysmenorrhoea.

A cost comparison of the product against available alternatives reveals the following:

Product	Dose Range	Cost (28 days)
Naproxen 250mg tablets (generic)	250mg three times a day	£3.06
Naproxen 250mg gastro-resistant tablets (generic)	250mg three times a day	£5.58
Naproxen 500mg tablets (generic)	500mg twice daily	£2.76
Naproxen 500mg gastro-resistant tablets (generic)	500mg twice daily	£8.85
Naproxen 125mg in 5ml oral suspension (*Tariff* special)	250mg (10ml) three times a day 500mg (20ml) to 1g (40ml) daily in two divided doses	£1,040.34 £693.56 to £1,387.12
Naproxen effervescent tablets 250mg (*Stirlescent*) (Stirling Health)	250mg three times a day 500mg to 1g daily in two divided doses	£33.18 £22.12 to £44.24
Ibuprofen oral suspension sugar free 100mg in 5ml (generic)	400mg (20ml) three times daily 600mg (30ml) three times daily	£22.17 £33.26
Ibuprofen oral suspension 100mg in 5ml (*Brufen Syrup*) (BGP Products)	400mg (20ml) three times daily 600mg (30ml) three times daily	£29.83 £44.75

PACEF Recommendations

Prescribers should consider low dose ibuprofen first line whenever an NSAID is indicated. Naproxen represents a suitable second line alternative, although GI risk is higher. Where naproxen is indicated, generic 250mg and 500mg tablets are preferred. In patients with swallowing difficulties, naproxen 125mg in 5ml oral suspension is prohibitively expensive and should not be prescribed; designation RED-RED and not approved for inclusion in the *Lincolnshire Joint Formulary*. Naproxen effervescent tablets 250mg (*Stirlescent*) are significantly higher in cost than naproxen tablets or gastro-resistant tablets, but lower in cost than the unlicensed liquid special. Ibuprofen oral suspension 100mg in 5ml is available on the *Lincolnshire Joint Formulary* and presents a preferred alternative at an equivalent cost. In view of this, naproxen effervescent tablets 250mg (*Stirlescent*) are designated RED-RED and are not approved for inclusion in the *Lincolnshire Joint Formulary*.

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

CANAGLIFLOZIN (*INVOKANA*, *VOKANAMET*): SIGNAL OF INCREASED RISK OF LOWER EXTREMITY AMPUTATIONS OBSERVED IN TRIAL IN HIGH CARDIOVASCULAR RISK PATIENTS

A signal of increased lower limb amputation (primarily of the toe) in people taking canagliflozin compared with placebo in a clinical trial in high cardiovascular risk patients is currently under investigation by the MHRA and the European Medicines Agency. We previously reported on EMA concerns in *PACE Bulletin* Volume 10 No 10 (July 2016).

This investigation was triggered when an increase in amputations, mostly toes, was observed in the canagliflozin groups 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 and MHRA review and no conclusion has yet been reached.

Advice for healthcare professionals:

- As a precaution, consider stopping canagliflozin if a patient develops a significant lower limb complication (e.g., skin ulcer, osteomyelitis, or gangrene), at least until the condition has resolved, and continue to monitor the patient closely.
- Carefully monitor patients receiving canagliflozin who have risk factors for amputation (e.g., previous amputations, existing peripheral vascular disease, or neuropathy)
- Monitor all patients for signs and symptoms of water or salt loss. Ensure patients stay sufficiently hydrated to prevent volume depletion in line with recommendations in the product information; note that diuretics can exacerbate dehydration
- Advise patients to: (1) stay well hydrated; (2) carry out routine preventive foot care; and (3) seek medical advice promptly if they develop skin ulceration, discolouration, or new pain or tenderness.
- Start treatment for foot problems (e.g., ulceration, infection, or new pain or tenderness) as early as possible.
- Continue to follow standard treatment guidelines for routine preventive foot care for people with diabetes

- Report side effects with canagliflozin or any other medicine to the MHRA on a Yellow Card.

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 should consider stopping canagliflozin in patients who develop significant foot problems.

NEXPLANON (ETONOGESTREL) CONTRACEPTIVE IMPLANTS: REPORTS OF DEVICE IN VASCULATURE AND LUNG

There have been rare reports of *Nexplanon* implants reaching the lung via the pulmonary artery. An implant that cannot be palpated at its insertion site in the arm should be located as soon as possible and removed at the earliest opportunity. If an implant cannot be located within the arm, perform chest imaging. Correct subdermal insertion reduces the risk of these events.

Background information

Nexplanon – Etonogestrel Implant 68mg - acts by preventing ovulation and is usually effective for 3 years. Safety and efficacy have been established in women between 18 and 40 years old. For maximum effectiveness *Nexplanon* needs to be correctly implanted by someone who is trained to fit it. The *Nexplanon* implant should be inserted subdermally just under the skin on the inner side of the upper arm.

Reports and potential risk factors

The number of reports of *Nexplanon* implants in the vasculature received by the licence-holder is estimated to be approximately 1.3 per million implants sold worldwide.
No definitive set of adverse reactions have been associated with these events. However some cases have been reported of:

- dyspnoea
- haematoma at the insertion site
- excessive bruising at the insertion site
- a combination of the above

No specific risk factors have been identified. Potential risk factors include:

- deep insertion
- insertion in an inappropriate site
- insertion in thin arms

Evidence from the literature shows that implants found in the vasculature can become endothelised into the pulmonary artery. If they are located early enough it is possible to remove them by an endovascular procedure. Women should therefore be shown how to locate the implant immediately following insertion and advised to check the position of the implant frequently for the first few months.

Expert removers' network

A network of healthcare professionals who are experienced in implant localisations and difficult removals is available for consultation. To request additional information on implant insertion and removal, contact the network on 01992 467272.

Updated advice for healthcare professionals:

- An implant should only be inserted subdermally and by a healthcare professional who has been appropriately trained and accredited
- Do not insert over the sulcus (groove) between the biceps and triceps.
- Take care to avoid insertion close to any blood vessels or nerve bundles (e.g. the ulnar nerve).
- Immediately after insertion, verify the presence of the implant by palpation.
- Show the woman how to locate the implant and advise her to do this frequently for the first few months; if she has any concerns she should return to the clinic for advice.
- Locate an implant that cannot be palpated (e.g. using imaging of the arm) and remove it at the earliest opportunity
- If an implant cannot be located in the arm by palpation or imaging, perform chest imaging.
- Surgical or endovascular procedures may be required to remove an implant from the chest.
- Review the updated instructions on how to correctly insert the implant, including an amended diagram that illustrates: (1) the correct angle on the arm for insertion and (2) how to view the needle to avoid deep insertion.
- Report any suspected side effects with *Nexplanon,* or any other medicine or medical device, on a Yellow Card, including difficulties with insertion or removal of *Nexplanon*.

PACEF Comment

Etonogestrel implant 68mg (*Nexplanon*) is classed as GREEN on the *Lincolnshire Joint Formulary*. The formulary entry advises *Nexplanon* training is required as the insertion device is different to *Implanon*, which was the previously licensed etonorgestrel containing implant. Prescribers previously accredited to insert the *Implanon* implant must be re-accredited to insert *Nexplanon*.

TOPICAL MICONAZOLE, INCLUDING ORAL GEL: REMINDER OF POTENTIAL FOR SERIOUS INTERACTIONS WITH WARFARIN

In view of reports of serious bleeding events in patients taking miconazole and warfarin, the MHRA are considering further measures to minimise the risk of potentially serious interactions between miconazole and warfarin.

Yellow Card reports

Up to 13 April 2016, the MHRA have received 146 Yellow Cards that report possible drug interactions between miconazole and warfarin. Most reports (128, 88%) concerned the oral gel form of miconazole. The most frequently reported events were: increased international normalised ratio (INR, 111 reports); contusion (21); haematuria (17); and epistaxis (8).

Approximately half of the 146 cases reported an INR increase above 10—i.e., the patient was at significantly increased risk of bleeding events (noting that the target INR range for a patient on long-term warfarin therapy is usually between 2 and 3). In 3 cases, a fatal outcome was reported as a result of a haemorrhagic event.

Latest MHRA review

The MHRA are currently reviewing available data for this interaction to determine whether further measures are required to minimise the risks to patients. This review follows a coroner's report of a death, which may have been partly due to the co-administration of miconazole oral gel and warfarin. Further advice will be communicated as appropriate when

the review is complete. Suspected drug interactions between miconazole and warfarin should be reported on a Yellow Card.

Reminder for healthcare professionals:

- Miconazole, including the topical gel formulation, can enhance the anticoagulant effect of warfarin—if miconazole and warfarin are used concurrently, the anticoagulant effect should be carefully monitored and, if necessary, the dose of warfarin reduced.
- Patients should be advised to tell their doctor or pharmacist if they are receiving warfarin before using products that contain miconazole (including those available without prescription), and to seek medical advice if they notice signs of over-anticoagulation during treatment, such as sudden unexplained bruising, nosebleeds or blood in the urine.

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