Greater East Midlands Commissioning Support Unit in association with
Lincolnshire Clinical Commissioning Groups, Lincolnshire Community Health Services,
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Lincolnshire Prescribing and Clinical Effectiveness Bulletin

Volume 8; Number 5 **March 2014**

What's new this month?

- **The MHRA have issued advice on the prescribing of antiepileptic drugs (AEDs) with particular emphasis on the risks of switching and the need to ensure continuity of supply with some agents. For AEDs in Categories 2 and 3 (the lower risk categories) specific advice is given on each agent as to whether generic prescribing and switching between products is appropriate (see page 2).**
- **Imiquimod 5% cream (*Aldara*) is re-designated AMBER without shared care for the treatment of adults with external genital and perianal warts, small superficial basal cell carcinomas or clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp. It should only be prescribed in primary care following initiation by or on the advice of a dermatologist. The product was previously designated RED and confined to dermatologist use only (see page 6).**
- **Lubiprostone 24 microgram capsules (*Amitiza*) are designated RED-RED for the treatment of chronic idiopathic constipation. Guidance on the management of constipation is provided (see pages 7 and 8).**
- **Both the *Lynlor* and *Shortec* formulations of oxycodone standard release capsules 5mg, 10mg and 20mg are designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary*. Prescribers are urged to review all prescribing of standard release oxycodone capsules to ensure that all prescriptions specify either *Lynlor* or *Shortec*. The potential annual saving across the county is over £60,000 (see page 9).**

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SUMMARY OF PACEF DECISIONS: *FEBRUARY 2014 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Imiquimod 5% cream (Aldara)	For the topical treatment of: external genital and perianal warts in adults; small superficial basal cell carcinomas (sBCCs) in adults; or clinically typical, non hyperkeratotic, nonhypertrophic actinic keratoses (AKs) on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are	Re-classified as AMBER without shared care within licensed indications. Can be prescribed in primary care subject to initiation by or on the advice of a dermatologist; already approved for use on the *Lincolnshire Joint Formulary.*

	contraindicated or less appropriate.	
Lubiprostone 24 microgram capsules (*Amitiza*)	For the treatment of chronic idiopathic constipation which has not responded to diet and other non-pharmacological measures.	RED-RED Not approved for inclusion in the *Lincolnshire Joint Formulary*.
Oxycodone standard release capsules 5mg, 10mg and 20mg (*Lynlor*)	For the treatment of severe pain requiring an opioid analgesic.	GREEN
Oxycodone standard release capsules 5mg.10mg and 20mg (*OxyNorm*)	For moderate to severe cancer pain or post-op pain. For the treatment of severe pain requiring a strong opioid.	*OxyNorm* should not be prescribed by brand name; lower cost equivalents are now available.
Oxycodone standard release capsules 5mg, 10mg and 20mg (*Shortec)*	For moderate to severe cancer pain or post-op pain. For the treatment of severe pain requiring a strong opioid.	GREEN

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 NHS in Lincolnshire website (www.lincolnshire.nhs.uk); follow the commissioning link to PACEF. Electronic copies of both the *PACE Bulletin* and our sister publication *PACE Shorts* (a short summary 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.

The *Lincolnshire Joint Formulary* is available on line and is fully searchable; it can be accessed at www.lincolnshirejointformulary.nhs.uk

ANTIEPILEPTIC DRUGS: NEW ADVICE ON SWITCHING BETWEEN DIFFERENT MANUFACTURERS' PRODUCTS FOR A PARTICULAR DRUG

The Medicines and Healthcare Products Regulatory Agency (MHRA) have issued advice on the prescribing of antiepileptic drugs (AEDs) with particular emphasis on the risks of switching and the need to ensure continuity of supply with some agents. For AEDs in Categories 2 and 3 (the lower risk categories) PACEF have developed specific advice on each agent advising on whether generic switching or standardization around generic products is appropriate.

Ordinarily, patent expiry and the emergence of lower cost generic versions of established branded products usually leads to low cost generic prescribing and a steep decline in the use of the originator brand. Any patient receiving a regular generic prescription on repeat will quickly realise that there are often a number of interchangeable generic products on the market for each medicine and that on a month to month basis they will see different manufacturers' products supplied from their practice or community pharmacy. Traditionally, there have been some areas of prescribing where real concerns over bioequivalence between different manufacturers' products have been raised and, where evidence suggests that this is a real concern, prescribers have been advised to prescribe by brand or ensure continuity of supply by requesting a particular manufacturers' product on the prescription.

In the November 2013 *Drug Safety Update*, the MHRA issued advice on prescribing of antiepileptic drugs (AEDs) with particular emphasis on the risks of switching and the need to ensure continuity of supply with some products. In particular, variation in bioavailability between different manufacturers' products can increase the risk of adverse effects or loss of seizure control for some drugs. In order to clarify this and minimize the risks, the MHRA have categorized AEDs into three risk groups:

Category	Drugs	MHRA guidance
1	phenytoin, carbamazepine, phenobarbital, primidone	For these drugs, doctors are advised to ensure that their patients are maintained on a specific manufacturers' product
2	valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate	For these drugs, the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history
3	levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin	For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer's product unless there are specific reasons such as patient anxiety and risk of confusion or dosing errors.

PACEF Recommendations:

Category 1: Prescribers should ensure that prescriptions for all medicines in this category consistently specify either a brand name or the name of a preferred manufacturer.

Category 2: Prescribers may wish to consider generic prescribing for patients receiving AEDs in this category unless seizure frequency, treatment history or other patient factors dictate otherwise. Where brand or supplier consistency is deemed to be necessary, the preferred manufacturer or brand name should be specified on the prescription. Brand name prescribing of topiramate (as *Topamax*) or lamotrigine (as *Lamictal*) increases costs significantly and should be reserved for those already stabilized on these products and deemed to be inappropriate for generic products due to seizure frequency or aspects of their treatment history. It has been estimated that prescribing all topiramate and lamotrigine as their originator brands would increase prescribing costs in Lincolnshire by £1.27Mpa. Specific advice on the appropriateness of generic prescribing for each of the key drugs is tabulated below.

Category 3: Prescribers may wish to consider generic prescribing for patients receiving AEDs in this category. Specific advice on the appropriateness of generic prescribing for each of the key drugs is tabulated below.

Category 2: *Antiepileptic drugs and generic prescribing*

Drug	Products Available	UK Medicines Information and London New Drugs Group Advice [PACEF advice in bold]
Clobazam 10mg tablets	Generics	There are no specific data to suggest that switching causes problems in clinical practice. **Consider generic prescribing; no need to specify a preferred manufacturer unless seizure frequency, treatment history or other patient factors dictate otherwise.**
Clonazepam tablets 500 microgram and 2mg	Generics *Rivotril*	There are no specific data to suggest that switching causes problems in clinical practice. **Consider generic prescribing; no need to specify a preferred manufacturer or brand unless seizure frequency, treatment history or other patient factors dictate otherwise.**
Eslicarbazepine tablets 800mg	*Zebinix*	There are no specific data on

	No generics available. Patent expiry: 2021	switching eslicarbazepine to generic as there are no generics currently available. **Prescribe generically by non-proprietary or approved name.**
Lamotrigine dispersible tablets 5mg, 25mg and 100mg; tablets 25mg, 50mg, 100mg and 200mg.	Generics *Lamictal* *Lamictal Dispersible*	There is a lot of evidence to support switching and a lot of countries have mandatory switch programmes. The Dept of Health issued a statement in support of switching in 2005. **Consider generic prescribing; no need to specify a preferred manufacturer or brand unless seizure frequency, treatment history or other patient factors dictate otherwise.**
Oxcarbazepine oral solution 300mg in 5ml, tablets 150mg, 300mg and 600mg	Generics *Trileptal* *Trileptal Suspension*	Limited evidence suggests that different formulations may not be bioequivalent. **Prescribers should specify either a preferred manufacturer or brand name.**
Perampanel tablets 2mg, 4mg, 6mg, 8mg, 10mg and 12mg	*Fycompa* No generics available	There are no specific data on switching perampanel to generic as there are no generics currently available. **Prescribe generically by non-proprietary or approved name.**
Retigabine tablets 50mg, 100mg, 200mg, 300mg and 400mg	*Trobalt* No generics available	There are no specific data on switching retigabine to generic as there are no generics currently available. **Prescribe generically by non-proprietary or approved name.**
Rufinamide tablets 100mg, 200mg and 400mg	*Inovelon* No generics available	There are no specific data on switching rufinamide to generic as there are no generics currently available. **Prescribe generically by non-proprietary or approved name.**
Sodium valproate capsules 150mg and 300mg; granules (sachet) 50mg, 100mg, 250mg, 500mg and 1g; modified release tablets 200mg, 300mg, 500mg; oral solution (liquid, syrup) 200mg in 5ml; tablets (crushable) 100mg; tablets (enteric coated) 200mg and 500mg	Generics *Epilim* *Epilim Crushable* *Epilim Syrup* *Epilim Liquid* *Epilim Chrono* *Epilim Chronosphere MR* *Episenta* *Episenta Granules*	There are a number of different salts that increase confusion about switching. Evidence in support of bioequivalence between formulations is scanty. **Prescribers should ensure that prescriptions for sodium valproate and its salts consistently specify the name of a preferred manufacturer or brand.**
Topiramate capsules (sprinkle) 15mg, 25mg and 50mg tablets 25mg, 50mg, 100mg and 200mg	Generics *Topamax* *Topamax Sprinkle*	Limited evidence supports cautious switching to generics in most patients. **Consider generic prescribing; no need to specify a preferred manufacturer or brand unless seizure frequency, treatment history or other patient factors dictate otherwise.**
Zonisamide capsules 25mg, 50mg and 100mg	*Zonegran* No generics available	There are no specific data on switching zonisamide to generic as there are no generics currently available. **Prescribe generically by non-proprietary or approved name.**

Category 3: ***Antiepileptic drugs and generic prescribing***

Drug	**Products Available**	**UK Medicines Information and London New Drugs Group Advice [PACEF advice in bold]**
Ethosuximide 250mg capsules Ethosuximide Syrup 250mg/5ml	Generics *Emeside* *Zarontin*	There are no specific data to suggest that switching causes problems in clinical practice. Ethosuximide is mostly used in paediatrics. **Consider generic prescribing.**
Gabapentin capsules 100mg, 300mg, 400mg Gabapentin tablets 600mg and 800mg	Generics *Neurontin*	There are no specific data to suggest that switching causes problems in clinical practice. Most gabapentin is used in neuropathic pain where dose is less critical than in epilepsy. Patient anxiety or risk of confusion or dosing errors will need to be taken into account. **Consider generic prescribing.**
Lacosamide tablets 50mg, 100mg, 150mg and 200mg; syrup 10mg/ml	Generics *Vimpat*	There are no specific data to suggest that switching causes problems in clinical practice. Patient anxiety or risk of confusion or dosing errors will need to be taken into account. **Consider generic prescribng.**
Levetiracetam tablets 250mg, 500mg, 750mg and 1000mg; oral solution 100mg/ml	Various generics *Keppra*	There are no specific data to suggest that switching causes problems in clinical practice. **Consider generic prescribing.**
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg	*Lyrica* No generics available. Patent expiry: 2018.	There is no specific data on switching branded pregabalin to generic as there are no generics currently available. Most pregabalin is used in neuropathic pain where dose is less critical than in epilepsy. **Prescribe generically by non-proprietary or approved name.**
Tiagabine 5mg, 10mg and 15mg tablets	*Gabitril* No generics at present although first patents have expired.	There is no specific data on switching branded tiagabine to generic as there are no generics currently available. **Prescribe generically by non-proprietary or approved name.**
Vigabatrin tablets 500mg and sachets 500mg	Generics *Sabril*	There is little evidence to support or oppose switching. Absence of evidence and use in refractory cases suggests that generic switching would be unwise. **Ensure that prescriptions for vigabatrin consistently specify the name of a preferred manufacturer.**

References:
MHRA *Drug Safety Update*, Vol 7, Issue 4, *Antiepileptic drugs: new advice on switching between different manufacturers' products for a particular drug* (November 2013).
UK Medicines Information and London New Drugs Group, The Use of Generic Anti-Epileptic Drugs in Patients with Epilepsy (updated January 2014).

NEW DRUG ASSESSMENT: *IMIQUIMOD 5% CREAM (ALDARA)*

Imiquimod 5% cream (Aldara) holds a marketing authorisation for the topical treatment of:

(1) External genital and perianal warts (condylomata acuminata) in adults;
(2) Small superficial basal cell carcinomas (sBCCs) in adults;
(3) Clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses (AKs) on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate.

PACEF reviewed supporting evidence for the use of imiquimod 5% cream in actinic keratosis. In two vehicle controlled double blind studies, imiquimod 5% cream three times a week demonstrated superiority to placebo in reducing lesions, although response rates, appear to be around 50%.

Supporting evidence for imiquimod 5% cream in sBCCs comes from the published pooled results from two USA based phase 3 vehicle controlled randomised trials. In these studies, imiquimod 5% cream applied five times a week and seven times a week demonstrated complete clearance rates of between 73 and 77% as assessed at 12 weeks post treatment. In these studies, the five times a week regimen was better tolerated in terms of local site reactions than the seven times a week regimen. As a result of this, imiquimod 5% cream is only licensed for use five times weekly for the treatment of sBCCs in the UK.

Supporting evidence for use in anogenital warts comes from two randomised double blind trials where imiquimod 5% cream demonstrated efficacy on total and partial clearance of anogenital warts.

Imiquimod 5% cream is associated with local reactions such as itching, burning sensation, and erythema. The systemic adverse effects most widely reported are myalgia, headache and flu like symptoms.

A cost comparison between alternatives for actinic keratosis reveals that imiquimod 5% cream is potentially more expensive than alternatives dependent upon duration of therapy:

Drug	**Dose range**	**Cost (£)**
Imiquimod 5% cream (*Aldara*)	Apply 3 times weekly for 4-8 weeks	£48.60 - £97.20 (12-24 sachets)
Diclofenac 3% and sodium hyaluronate 2.5% gel (*Solareze*)	Apply twice daily for 60-90 days.	£38.30-£76.60 (50g-100g)
5-flurouracil 5% cream (*Efudix*)	Apply once or twice daily for 3-4 weeks	£32.90 (40g)
Ingenol mebutate (*Picato*) 500mcg/g 2 day course 150mcg/g 3 day course	Trunk and extremities: Apply contents of one 500mcg/g tube once daily for 2 days. Face and scalp: Apply contents of one 150mcg/g tube once daily for 3 days.	£65.00 2 day or 3 day treatment course
Fluouracil 0.5%, salicylic acid 10% solution (*Actikerall*)	Apply once daily for up to 12 weeks	£76.60 (2 x 25ml)

PACEF Recommendation

PACEF have previously designated imiquimod 5% cream (*Aldara*) as RED, for dermatologist use only. Following this re-assessment, imiquimod 5% cream (Aldara) is re-classified as AMBER without shared care within licensed indications. It can be prescribed in primary care subject to initiation by or on the advice of a dermatologist; it is already approved for use on the *Lincolnshire Joint Formulary.* Further written guidance from ULH Dermatologists is in preparation.

NEW DRUG ASSESSMENT: *LUBIPROSTONE 24 MICROGRAM CAPSULES (AMITIZA)*

Lubiprostone is a prostone, a locally acting chloride channel activator that enhances a chloride-rich intestinal fluid secretion without altering electrolyte concentrations in the serum. By increasing intestinal fluid secretion, lubiprostone increases motility in the intestine, thereby facilitating the passage of stool and alleviating symptoms associated with chronic idiopathic constipation. It has a marketing authorisation for the treatment of chronic idiopathic constipation which has not responded to diet and other non-pharmacological measures.

PACEF reviewed supporting clinical evidence from three pivotal trials which demonstrated that the 48mcg dose of lubiprostone is significantly more effective than placebo in the relief of constipation and associated symptoms. These trials were of short duration (4 weeks) and placebo controlled; there are no published trials comparing lubiprostone with any other laxative. The licensing authority noted that treatment efficacy diminishes after 4 weeks and have restricted the licensed indication to two weeks' duration. It is unclear as to how long the benefits of a two week course would last or whether there are any restrictions on the number and frequency of repeat two week courses that could be used.

The most common adverse effects are nausea which affects nearly a quarter of patients. Other common adverse effects include gastro-intestinal disturbances (diarrhoea, abdominal distension, pain, discomfort, flatulence and dyspepsia), palpitations, oedema, chest discomfort, headache, dizziness, dyspnoea, hyperhidrosis and hot flushes. Lubiprostone is contraindicated in patients with a known or suspected mechanical gastrointestinal obstruction.

A cost comparison reveals that lubiprostone is much more expensive than widely prescribed first and second line alternatives and comparably priced with prucalopride (*Resolor*):

Drug	Dose	Cost (£)
Lubiprostone 24 microgram capsules (*Amitiza*)	24mcg twice daily for 2 weeks	£59.36 (56 capsules; only available as a 4 week pack)
Prucalopride 2mg tablets (*Resolor*)	2mg once daily; reassess if no response after 4 weeks.	£59.52 (28)
Ispaghula husk (*Ispagel*) sachets	1 sachet one to three times daily	£1.69 (30 x 3.5g sachets)
Docusate sodium 100mg capsules (Dioctyl)	Up to 500mg daily in divided doses	£6.98(100 capsules)
Bisacodyl 5mg tablets	5mg-10mg at night	£3.43 (100)
Senna 7.5mg tablets	2-4 tablets at bedtime	£10.11 (60)
Lactulose 3.1 – 3.7g per 5ml oral solution	15ml once or twice daily	£3.09 (500ml)
Macrogol 3350 13.125g sachets (*Laxido Orange*)	1-3 sachets daily	£5.34(30)

PACEF Recommendation:

PACEF are concerned about the lack of comparative evidence between lubiprostone and any other alternative treatment for constipation. The cost of the product is also prohibitive, particularly as it is authorized for use in 2 week courses but only available in a 4 week pack. Prescribers are reminded of standard PACEF advice on the management of constipation previously published in *PACE Bulletin* Volume 5 No 7 (April 2011) (see Postscript: *Management of Constipation*). As a result of this, lubiprostone 24 microgram capsules (*Amitiza*) are designated RED-RED and have not been approved for inclusion in the *Lincolnshire Joint Formulary*. This evaluation will be reviewed and updated following publication of a forthcoming NICE Technology Appraisal of the product which is due to be published in the Autumn.

Management of Constipation

A recent *MeReC Bulletin* on the management of constipation (Vol 21 No 2 (January 2011)) identified the following key steps:

1. Advise about lifestyle measures (e.g. balanced diet, including dietary fibre, regular meals, adequate fluid intake, exercise).
2. If dietary measures are ineffective after 4 weeks or while waiting for them to take effect, offer additional oral laxatives.
3. Start treatment with a bulk forming laxative (soluble fibre) ensuring adequate fluid intake (e.g. ispaghula 3.5g sachets (*Fybogel*))
4. If stools remain hard, add or switch to an osmotic laxative (e.g. lactulose solution, polyethylene glycol).
5. If stools are soft but difficult to pass or if emptying is inadequate, add a stimulant laxative (e.g. bisacodyl EC tablets 5mg or senna tablets).
6. Advise that laxatives can be stopped once the stool becomes soft and passes easily. Doses should be reduced in a gradual manner.
7.In general, the smallest effective dose should be prescribed for the shortest time.
8. Prolonged treatment with laxatives is seldom necessary (exceptions might be where there are medical causes, where a constipating drug cannot be stopped and in children when laxatives may be continued for several months to avoid relapse). Where long-term control of constipation is considered necessary, bulk forming laxatives are preferred.
9. Only limited evidence supports the use of lactulose in chronic constipation. A Cochrane review concluded that polyethylene glycol (PEG) is superior to lactulose in terms of increasing stool frequency, improving stool form and reducing the need for additional products.
10. Stimulant laxatives should be considered before bulking agents where constipation results from lack of mobility (e.g. constipation in the elderly or disabled).
10. In pregnancy, where dietary and lifestyle measures fail, bulking agents (soluble fibre) are preferred.
11.Prucalopride has a role in women with chronic constipation for whom treatment with at least two laxatives from different classes, at the highest tolerated recommended doses for at least 6 months, has failed to provide adequate relief and invasive treatment for constipation is being considered. It should only be initiated by a clinician with experience in treating chronic constipation.

RAPID COST COMPARISON: *OXYCODONE STANDARD RELEASE CAPSULES (OXYNORM VS LYNLOR VS SHORTEC)*

Two new lower cost branded formulations of standard release oxycodone are now available: *Lynlor* and Shortec 5mg, 10mg and 20mg capsules.

A cost comparison with the brand leader *OxyNorm* reveals that both of the new products are 30% lower in cost than the brand leader:

Product	Strength	Cost (£) (56)
Oxycodone standard release capsules (*Shortec*)	5mg	£8.00
	10mg	£16.00
	20mg	£32.00
Oxycodone standard release capsules (*Lynlor*)	5mg	£8.00
	10mg	£16.00
	20mg	£32.00
Oxycodone standard release capsules (*OxyNorm*)	5mg	£11.43
	10mg	£22.86
	20mg	£45.71

Shortec and *Lynlor* are distributed through the following wholesalers: Phoenix Healthcare, Alliance Healthcare (Distribution) Ltd and AAH Pharmaceuticals Ltd. *Lynlor i*s also stocked by Maltbys and Mawdsleys.

If all of the standard release oxycodone prescribed in Lincolnshire were prescribed as *Lynlor* or *Shortec* the potential annual savings to the Lincolnshire CCGs would be as follows:

	Potential Annual Saving
East Lincolnshire CCG	£19,670
Lincolnshire West CCG	£26,000
South Lincolnshire CCG	£5,144
South West Lincolnshire CCG	£10,328
Lincolnshire	£61,142

PACEF Recommendation

Both the *Lynlor* and *Shortec* formulations of oxycodone standard release capsules 5mg, 10mg and 20mg are designated GREEN and approved for inclusion in the *Lincolnshire Joint Formulary.* Prescribers are urged to review all prescribing of standard release oxycodone capsules to ensure that all prescriptions specify either *Lynlor* or *Shortec*.

Acknowledgements

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