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PRESCRIBING AND DISPENSING PREGABALIN FOR NEUROPATHIC PAIN

Key Points

- In response to a High Court ruling, NHS England has issued guidance to Clinical Commissioning Groups for onward transmission to prescribers regarding the prescribing and dispensing of pregabalin. Similar guidance has also been communicated to community pharmacists through the NHS Business Services Authority.
- NHS England pregabalin guidance reads as follows: ‘In view of Warner-Lambert’s patent rights, pregabalin should only be prescribed for the treatment of neuropathic pain under the brand name *Lyrica* (unless there are contra-indications or other special clinical needs, for example allergy related to an excipient or supply problems with the branded product etc)’.
- When prescribing pregabalin for the treatment of anything other than central or peripheral neuropathic pain, pregabalin should be prescribed generically.
- Early indications are that new pregabalin generic preparations are priced at 75% of the *Lyrica* brand price, although it is uncertain as to how quickly NHS reimbursement prices will fall to reflect this. At present, pregabalin capsules are in Category C with the reimbursement prices based on the *Lyrica* prices.
- Prescribers should ensure that, as far as reasonably possible, branded *Lyrica* is 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).
- 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.
- 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.
- Pregabalin can continue to be prescribed generically 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).
- New lower cost branded formulations of pregabalin are now available, but should only be prescribed for non-patent protected indications.

- Where pregabalin is prescribed, either as *Lyrica* or as a new lower cost alternative brand, considerable savings can still be made by optimising the dosage from three times daily to twice daily while maintaining total daily dose.. Similar opportunities to optimise dosage and generate significant savings exist across the range of strengths and doses for both *Lyrica* and alternative lower cost brands (see cost comparison table below). Savings can also be realised by rationalising prescribed doses into the fewest number of tablets (i.e. one 100mg capsule rather than two 50mg capsules).
- 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. An equivalent dose table between pregabalin and gabapentin is included as part of this *Bulletin*.

Background

Not all generic medicines come to market with the full range of marketing authorisations that are held by the originator product. It is relatively common for a pharmaceutical company to launch a product for one patent protected indication only to gain a patent and marketing authorisation for a subsequent indication or indications at a later date. Examples from the relatively recent past include: omeprazole (*Losec*), clopidogrel (*Plavix*) and atorvastatin (*Lipitor*). When the original patent expires, generic alternatives licensed for the original patented indication can be launched. These products will not be licensed for subsequently patented indications and will not hold the full range of marketing authorisations held by the originator brand. European medicines legislation specifically allows for the marketing of so-called ‘skinny labelled’ generic drugs by allowing product information, such as summaries of product characteristics (SPCs) and patient information leaflets (PILs), to only include indications, dosage directions and dosage forms relevant to the patent that has expired. For example, when generic clopidogrel (*Plavix*) first became available, skinny labelled generics made no reference in the product information to the treatment of acute coronary syndrome in combination with aspirin and were not licensed in the first instance for this patent protected indication. This issue has arisen again in 2014/15 with the patent expiry of certain licensed indications for pregabalin (*Lyrica*).

What are the patent expired indications for pregabalin? And what are the patent protected indications?

	Patent expired indications	Patent protected indications
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (<i>Lyrica</i>)	Epilepsy Generalised anxiety disorder	Neuropathic pain

Specifically, patent protection remains in force for the use of *Lyrica* in ‘the treatment of peripheral and central neuropathic pain in adults’. Following a High Court judgement in favour of Warner-Lambert Company LLC (a member of the Pfizer group of companies), NHS England has issued guidance to Clinical Commissioning Groups for onward transmission to prescribers regarding the prescribing and dispensing of pregabalin. Similar guidance has also been communicated to community pharmacists through the NHS Business Services Authority.

What does NHS England guidance state?

1. In view of Warner-Lambert's patent rights, **pregabalin should only be prescribed for the treatment of neuropathic pain under the brand name *Lyrica*** (unless there are contra-indications or other special clinical needs, for example allergy related to an excipient or supply problems with the branded product etc).
2. When prescribing pregabalin for the treatment of anything other than neuropathic pain, pregabalin should be prescribed generically.
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.

PACEF Recommendations:

(1)When prescribing pregabalin for the treatment of anything other than central or peripheral neuropathic pain, pregabalin should be prescribed generically.

(2)Prescribers should ensure that, as far as reasonably possible, branded *Lyrica* is 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).

(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 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)New lower cost branded formulations of pregabalin are now available, but should only be prescribed for non-patent protected indications.

How is neuropathic pain defined?

NICE Clinical Guideline 173: *Neuropathic pain – pharmacological pain* (November 2013) defines neuropathic pain as 'pain caused by a lesion or disease of the somatosensory nervous system'. Examples of common conditions that have peripheral neuropathic pain as a symptom are painful diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, radicular pain, post-surgical chronic neuropathic pain and neuropathic cancer pain (such as chemotherapy induced neuropathy, neuropathy secondary to tumour antigens or caused by direct invasion or compression of neural structures). Examples of conditions that can cause central neuropathic pain include stroke, spinal cord injury and multiple sclerosis.

Typical descriptions of neuropathic pain include terms such as shooting, stabbing, like an electric shock, burning, tingling, tight, numb, prickling, itching and a sensation of pins and needles.

Which are the new pregabalin generic preparations and what are they licensed for?

	Licensed indications
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (<i>Lecaent</i>) (Actavis)	<i>Epilepsy</i> <i>Lecaent</i> is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation. <i>Generalised Anxiety Disorder</i> <i>Lecaent</i> is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.
Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (<i>Rewisca</i>) (Consilient Health Ltd)	<i>Epilepsy</i> <i>Rewisca</i> is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation. <i>Generalised Anxiety Disorder</i> <i>Rewisca</i> is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

Other generic pregabalin preparations from a range of different companies (including Dr Reddy's, Teva, Mylan and Sandoz) are likely to be available soon.

What is the current legal situation?

Actavis have commenced court proceedings against Warner Lambert Company LLC seeking the revocation of the patent protecting *Lyricea* for use in neuropathic pain. Warner Lambert consider that some of the activities of Actavis to date have infringed their neuropathic pain patent. It is expected that this case will come to court in June 2015. In the meantime the patent remains in place and NHS England guidance has been published. As you may be aware, Pfizer wrote to practices, pharmacies and local NHS opinion leaders in December 2014 suggesting that those guilty of prescribing generic pregabalin for neuropathic pain, dispensing generic pregabalin for neuropathic pain or issuing guidance supportive of generic prescribing of pregabalin for neuropathic pain could be prosecuted for procurement of patent infringement. If the court find in favour of Actavis later in the year, the company have communicated to all prescribers their intention to launch a generic pregabalin product licensed for the treatment of neuropathic pain in addition to epilepsy and GAD. In the event that circumstances change to this extent, PACEF will issue revised guidance. In the meantime, prescribers, pharmacists and dispensers are advised to follow NHS England guidance.

How does this affect community pharmacists?

In common with prescribers, pharmacists are obliged to ensure that the *Lyricea* brand of pregabalin is dispensed for all patients prescribed the treatment for the patent protected indication of neuropathic pain. To this end community pharmacists are likely to contact their local surgeries asking prescribers to ensure that prescriptions for pregabalin for patients with neuropathic pain are prescribed as the *Lyricea* brand. Some pharmacies have already contacted practices in an attempt to establish ground rules. Practices are asked to be supportive of community pharmacies requesting script changes from generic to brand for those patients prescribed generic pregabalin for a patent protected indication. Compliance with such requests will ensure that neither the prescriber nor the dispensing pharmacist is guilty of patent infringement. There is no requirement for the pharmacist to make inquiries relating to the medical condition being treated for particular individuals, although agreeing a common approach that recognizes the need to respect the patent by both the prescriber and

the dispensing pharmacist is likely to be helpful. To some extent, community pharmacies will already be aware of the indication for prescribing pregabalin for some patients either from their own patient medication records or information acquired from medicines use review or through regular interaction with the patient or carer. Assuming the generic reimbursement price of pregabalin begins to fall, community pharmacies will find themselves increasingly compromised if branded *Lyrica* has to be supplied against an open generic prescription for pregabalin for a patent protected indication that the prescriber is unwilling to change.

How quickly will the cost of prescribing pregabalin begin to fall?

In the current *Drug Tariff* (March 2015), pregabalin capsule formulations are still classified as Category C (i.e. drugs that are not readily available as a generic) with the reimbursement price based on the price of the originator brand *Lyrica*. This means that, in the short term, generically prescribed pregabalin and brand prescribed *Lyrica* are likely to continue to be reimbursed at the *Lyrica* price. As the number of generically available pregabalin preparations increases, there is a possibility that generic pregabalin preparations will move into Category M and prices will begin to fall, although it is difficult to predict how quickly this will happen.

At present, the only ways to reduce pregabalin prescribing costs are: (1) prescribing lower cost branded pregabalin preparations by brand for non-patent protected indications; (2) dose and strength optimisation of existing pregabalin prescriptions; (3) consideration of alternative therapies such as gabapentin and; (4) continuing to prescribe pregabalin generically for non-patent protected indications in the expectation that the generic reimbursement price of pregabalin will eventually fall (see (1) below).

(1) Prescribing lower cost branded pregabalin preparations by brand for non-patent protected indications;

At present, published prices of new lower cost branded pregabalin formulations, such as *Rewisca* and *Lecaent*, are 75% of established *Lyrica* prices strength for strength. In March 2015, *Drug Tariff* reimbursement prices for pregabalin capsules (various strengths) are still based on the price of *Lyrica*, the originator brand. This means that the reimbursement price for pregabalin capsules prescribed either generically or as the *Lyrica* brand will remain at the *Lyrica* price until the *Tariff* price changes. Only branded prescribing of the lower cost brands will be reimbursed at the lower price. While there is a saving associated with brand name prescribing of the new low cost brands in the short-term, it is hard to predict how the market place will change in the coming months.

PACEF Recommendation:

At present, prescribers are advised to focus on ensuring that all pregabalin prescribing for non-patent protected indications remains generic with *Lyrica* is prescribed by brand solely for central and peripheral neuropathic pain. Once the generic reimbursement price of pregabalin begins to fall, fortuitous savings will begin to accumulate for non-patent protected indications.

(2) Dose and strength optimisation

Where pregabalin is prescribed, either as *Lyrica* or as a new lower cost alternative brand, considerable savings can still be made by optimising the dosage from three times daily to twice daily while maintaining total daily dose. For example, *Lyrica* 50mg three times daily (150mg total daily dose) costs £96.60 for 28 days' supply while 75mg twice daily (still 150mg t.d.d.) costs £64.40, a saving of £32.20 every 28 days or £418.60 per patient per year. Similar opportunities to optimise dosage and generate significant savings exist across

the range of strengths and doses for both *Lyrica* and alternative lower cost brands (see cost comparison table below). Savings can also be realised by rationalising prescribed doses into the fewest number of tablets (i.e. one 100mg capsule rather than two 50mg capsules).

(3) Consideration of alternative therapies

The gamma amino butyric acid (GABA) analogues, pregabalin and gabapentin are related both structurally and pharmacologically. Gabapentin is licensed for:

- monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation.
- peripheral neuropathic pain.

The NICE Clinical Guideline on the management of neuropathic pain recommends amitriptyline (off-label), duloxetine, gabapentin or pregabalin as safe and cost-effective alternatives. NICE recommend that choice of treatment should be made on an individual basis. There is one small trial comparing pregabalin and gabapentin in patients with neuropathic cancer pain, the results of which were compromised by failure to use maximal doses of each comparator. A recent systematic review and meta-analysis concluded that tricyclic antidepressants, duloxetine, gabapentin and pregabalin were all potential first line alternatives for neuropathic pain. Similar Numbers Needed to Treat (NNTs) were calculated for pregabalin (7.7) and gabapentin (7.2).

PACEF Recommendation

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.

Equivalent doses of pregabalin and gabapentin in patients with normal renal function

<u>Pregabalin total daily dose pre-switch</u>	<u>Suggested equivalent dose of gabapentin</u>
150mg	300mg three times daily
225mg	400mg three times daily
300mg	600mg three times daily
450mg	2 x 400mg three times daily
600mg	3 x 300mg three times daily

For daily doses of pregabalin below 150mg daily (e.g. 75mg or 100mg) switch to gabapentin 100mg three times daily and titrate up if necessary.

Cost Comparison

	<u>Dose</u>	<u>Cost (28 Days)</u>
Pregabalin 75mg capsules (<i>Rewisca</i>)	75mg twice daily	£48.30
Pregabalin 75mg capsules (<i>Lyrica</i>)	75mg twice daily	£64.40
Gabapentin 300mg capsules	300mg three times daily	£3.49
Pregabalin 50mg capsules (<i>Rewisca</i>)	50mg three times daily	£72.45
Pregabalin 50mg capsules (<i>Lyrica</i>)	50mg three times daily	£96.60

Gabapentin 300mg capsules	300mg three times daily	£3.49
Pregabalin 100mg capsules (<i>Rewisca</i>)	100mg three times daily	£72.45
Pregabalin 100mg capsules (<i>Lyrica</i>)	100mg three times daily	£96.60
Gabapentin 600mg tablets	600mg three times daily	£8.16
Pregabalin 150mg capsules (<i>Rewisca</i>)	150mg twice daily	£48.30
Pregabalin 150mg capsules (<i>Lyrica</i>)	150mg twice daily	£64.40
Gabapentin 600mg tablets	600mg three times daily	£8.16
Pregabalin 200mg capsules (<i>Rewisca</i>)	200mg three times daily	£72.45
Pregabalin 200mg capsules (<i>Lyrica</i>)	200mg three times daily	£96.60
Gabapentin 300mg capsules	THREE 300mg (900mg) capsules three times daily	£10.47
Pregabalin 300mg capsules (<i>Rewisca</i>)	300mg twice daily	£48.30
Pregabalin 300mg capsules (<i>Lyrica</i>)	300mg twice daily	£64.40
Gabapentin 300mg capsules	THREE 300mg (900mg) capsules three times daily	£10.47

N.B. Both gabapentin and pregabalin require dosage reduction in the renally impaired. See *BNF* for details.

References

Actavis UK Ltd, Summary of Product Characteristics: Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (*Lecaent*)
Communication from Actavis to All Prescribers, *Important information when prescribing pregabalin* (March 2015).
Consilient Health Ltd, Summary of Product Characteristics: Pregabalin capsules 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg (*Rewisca*)
High Court Judgement from The Honourable Mr Justice Arnold: Warner Lambert Company LLC vs Actavis Group (2nd March 2015)
NHS England, *Schedule 1: The Pregabalin Guidance (NHSE Gateway Reference: 03126)* (March 2015)
NICE Clinical Guideline 173, *Neuropathic pain: The pharmacological management of neuropathic pain in adults in non-specialist settings* (November 2013)
Trent Medicines Information Service, QIPP Detail Aid: *Gabapentin or pregabalin for neuropathic pain* (updated March 2015)

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Stephen Gibson
Head of Prescribing and Medicines Optimisation
Greater East Midlands Commissioning Support Unit

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