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# Generic pregabalin; current situation and implications for health authorities, generics and biosimilars manufacturers in the future

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**Introduction:** The manufacturer of pregabalin has a second use patent covering prescribing for neuropathic pain – its principal indication. The manufacturer has threatened legal action in the UK if generic pregabalin rather than Lyrica is prescribed for this indication. No problems exist for practitioners who prescribe pregabalin for epilepsy or generalized anxiety disorder. This has serious implications for health authorities. In Germany, however, historically generics can be legally prescribed for any approved indication once one indication loses its patent.

**Aim:** To establish the current situation with pregabalin among health authorities principally from European countries.

**Methods:** Personnel from 33 regional and national health authorities mainly from Europe, and nine from universities across Europe working as advisers to health authorities or with insight into their activities, were surveyed regarding four specific questions via email to shed light on the current situation with Lyrica and pregabalin in their country. The information collated from each country was subsequently checked for accuracy with each co-author by email and face-to-face contact, and collated into five tables.

**Results:** The scenarios ranged from extending the patent life of Lyrica, e.g. France, endorsing the prescribing of Lyrica for neuropathic pain at the same price as the generic drug, e.g. Catalonia and South Korea, and current prescribing of pregabalin for all indications, e.g. Germany and Serbia. Little activity has taken place in European countries in which generic pregabalin is not yet reimbursed.

**Conclusion:** The availability of generic pregabalin has prompted a number of different activities to be undertaken among the 33 countries and regions surveyed. The situation in Serbia and the historic situation in Germany provide examples of ways to maximize savings once a product loses its patent for at least one indication.

**Keywords:** Generics, health authorities, Lyrica, pregabalin

## Introduction

The increased use of generic medicines is essential to sustain healthcare systems given the ever-increasing pressure on resources [1-4]. Prices of generic drugs are as low as 2–10% of pre-patent loss prices in some countries [5-7]. Consequently, increased use of generic drugs can generate substantial savings, which can be redirected into funding new valued high-priced medicines [2, 5-12], which is especially important for countries struggling to fund these medicines. A number of strategies globally have been initiated to encourage prescribing and dispensing of generic drugs rather than the originator (brand-name) drug, as well as patented products in a class in which all medicines are seen as essentially similar at therapeutically equivalent doses [4, 8-12].

Increasing use of generic drugs does not appear to compromise care, and many studies have reported little or no difference in outcomes across a range of products and classes [13-18]. In Europe, only generic drugs produced in accordance with the European Medicines Agency's strict guidelines and definitions [19] are granted marketing authorization.

Well-known and agreed exceptions to generics prescribing or substitution include lithium, theophyllines, some anti-epileptic drugs, modified release preparations and immunosuppressants. In these cases, brand-name prescribing is endorsed [20-23]. Agreed exceptions to generics prescribing, including medicines to treat epilepsy and prevent organ rejection, also exist in Germany and Sweden [6, 24].

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A new emerging problem, however, has come to the fore in recent years, concerning the expiry of patents for medicines that have patents for more than one indication, and the threat of legal action by the manufacturer of the originator drug against physicians. This situation occurred recently in the case of pregabalin for the treatment of epilepsy and generalized anxiety disorder (GAD) when the basic patent for pregabalin expired in July 2014 in a number of European countries. The patent for its second medical use, protecting the originator drug Lyrica's use in treating neuropathic pain, extends to July 2017 in Europe [25, 26]. In the UK, this resulted in the manufacturer of the originator drug (Lyrica) claiming patent infringement and warning doctors not to prescribe the generic drug pregabalin for neuropathic pain [26, 27]. As far as we are aware, this is the first time this has happened, and has serious implications for health authorities.

Prior to this, the originator manufacturer of Lyrica had been fined heavily for promoting gabapentin (prelude to pregabalin) off label for the treatment of neuropathic pain [28-31], although it is now recommended for this indication [32]. In addition, there have been concerns with the methodological limitation of some of the studies of pregabalin in neuropathic pain [33-35]. Pregabalin, for example, is currently not listed in the 'Wise List' of Stockholm Metropolitan Healthcare Region because of efficacy and safety concerns compared with other treatments for these conditions [36]. However, there are increasing concerns with the implications of the activities of second use patents with Lyrica [26, 37].

In this paper, historical developments in Germany and the UK relating to this case are examined. Personnel from regional and national health authorities from principally across Europe, and advisers to health authorities working in universities, were then surveyed to ascertain the current situation with pregabalin in their country and to determine the best strategy for maximizing savings for countries once a product loses its patent for any indication.

### United Kingdom

In the UK, the international non-proprietary name (INN) prescribing rate is over 80%, and up to 98-99% of non-contentious generic drugs, such as proton pump inhibitors, renin-angiotensin inhibitors and statins, with pharmacists not permitted to substitute an originator drug with a generic drug when the originator drug is prescribed [7, 20, 21, 38].

The UK medicines agency recently issued advice on which epilepsy drugs to prescribe by brand name (originator) and which by INN [39]. Pregabalin was considered suitable for INN prescribing [39], which was endorsed by the originator company stating 'there will be no clinical superiority of the originator branded medicine Lyrica over generic pregabalin' [25].

The extended patent for neuropathic pain resulted in the originator company writing to all Clinical Commissioning Groups (CCGs) in England and Health Boards in Scotland in November 2014 pointing out that generics of pregabalin were expected to be approved only for GAD and epilepsy indications, and that the prescribing of generic pregabalin for neuropathic pain could represent 'off-label' use. This would be considered a patent

infringement constituting an unlawful act, with the originator company reserving all legal rights in this regard [25-27].

The wish of generics companies to make generic pregabalin available in the UK across all indications resulted in a court case, with the originator company as claimant and the Actavis group as the principal defendant [26, 40]. The judge in his deliberations, posted on 21 January 2015, granted Actavis the possibility to launch generic pregabalin and again stated that the best way forward was to try to ensure physicians prescribe Lyrica for the treatment of neuropathic pain and pregabalin for other conditions, including epilepsy [40, 41].

The actions of the originator company are unsurprising. In 2013, global sales of Lyrica generated US\$4.6 billion for the company [40]. In the UK, sales of Lyrica increased by 53% between 2011 and 2013 to about US\$310 million. It is estimated that 54% of prescriptions in September 2014 were for treating pain, of which 44% was for neuropathic pain [40]. In 2014, sales of Lyrica were GBP 250 million (US\$390 million) [26]. The potential loss in revenue, therefore, would hugely impact company sales – estimated to be GBP 220 million per year (US\$340 million) across all indications assuming high INN prescribing rates and generic drug prices rapidly falling by 90% of the price of Lyrica [7, 42].

In an attempt to preserve sales of Lyrica, the originator company has been proactive in lobbying groups in the UK who could influence physician prescribing, such as the Medicine Management groups within CCGs, the Pharmaceutical Services Negotiating Committee, the General Practitioners Committee of the British Medical Association, and the National Health Service [26, 32, 37, 43-45]. For instance, National Health Service (NHS) England in March 2015 issued advice to all CCGs that within electronic prescription systems there should be a notice or advice box stating '*If treating neuropathic pain, prescribe Lyrica (brand) due to patent protection. For all other indications, prescribe generically*' [45]. The Pharmaceutical Services Negotiating Committee stated to its members they should be aware that the originator company still retains the indication for neuropathic pain. Members were also made aware that following a high court decision, 'it was agreed by all parties that the generic [drug] producers would write to CCGs to ensure they were aware that the generic [drug] could not be supplied for the patented indication. A CCG or other party that promotes the supply of generic pregabalin for the patented indication risks facing legal action' [43].

This situation in the UK has important future implications for generics and biosimilars companies across countries, as it may impede the ability of health authorities to fully realize potential savings from generics and biosimilars once the first indication loses its patent, especially if pharmaceutical companies look to extend the number of indications for their new medicines once launched in an attempt to extend the patent life.

### Germany

Germany has taken a different approach to the UK. Currently, nine pregabalin generics are available and reimbursed in Germany (up to April 2015), all of which have the indications for epilepsy and anxiety disorders. The situation, however, is now less clear cut as the originator manufacturer, has

taken Ratiopharm, Hexal, 1A Pharma, Glenmark and Aliud Pharma and some Sickness Funds (German payers) to court in an attempt to conserve Lyrica sales for neuropathic pain (up to 10 April 2015) [46]. The legal battle is still ongoing. The originator company's previous strategy to promote Lyrica was to communicate directly with physicians or via KVs (regional doctors' associations) by letter, making it clear that Lyrica was the only pregabalin licensed for neuropathic pain [47]. However, these communications were largely dismissed by KVs because the focus was on legal rather than medical issues, and the KVs continued to advise physicians to reach targets of generics prescribing of at least 85%. In addition, the Social Code Book V (SGB V), which is decisive for Sickness Funds, stated in paragraph 129 that generics substitution is possible wherever at least one indication matches [48-50].

The contrast between the situation in the UK and the situation in Germany, and the implications for potential savings when other pharmaceutical products lose their patents for some but not all indications, has led health authorities, across Europe, to review the current status of pregabalin in other countries in order to refine their own strategies if possible.

### Aim of study

A qualitative study was undertaken to ascertain the current situation between generic pregabalin and Lyrica among health authorities principally from across Europe. This included a range of Central, Eastern and Western European countries with different epidemiology and funding of health care, as well as policies to enhance the prescribing of generics. This builds on the situation Germany and the UK, and is in line with current recommendations for conducting cross-national research projects [51]. The aim was to maximize future savings for countries once a product loses its patent for any indication.

### Materials and methods

Personnel from 33 regional and national health authorities mainly from across Europe, and personnel from nine universities working closely as advisers to health authorities or with insight into health authority activities, were contacted by email to provide answers to the following four questions (up to April 2015):

1. Are you aware of any similar examples to the situation of pregabalin and Lyrica in the UK from other pharmaceutical companies for small molecules once the patent has been lost (biosimilars are a different issue)? If so, what were these and how were they handled (if at all).
2. Was Lyrica reimbursed in your country? If yes, for what indications?
3. Has generic pregabalin been launched in your country/about to be launched? If yes what date (month) and indications?
4. Has the originator company issued a letter to healthcare professionals in your country similar to the letter issued to CCGs in the UK? If yes, what actions (if any) are being taken?

This was supplemented with knowledge from other high-income countries taking different approaches to the availability of generic pregabalin to potentially provide additional examples.

All health authority personnel are involved with either pricing and reimbursement decisions, decisions concerning funding or

monitoring the use of medicines, or both, including generics, in their countries and regions. Consequently, it was felt that they would have the most insight into the current situation concerning pregabalin and Lyrica in their countries and regions. European countries included those from Central, Eastern and Western Europe to ensure legitimacy with the findings. Personnel from regions in The Netherlands, Sweden and the UK were also included, as healthcare budgets in these countries are devolved downwards.

The written information supplied by the co-authors and others for each of the questions for each country was collated and summarized by the corresponding author. The summarized information was subsequently checked via email and face-to-face contact with the relevant co-author(s) to ensure the accuracy of the summarized information. The information supplied was subsequently summarized into five categories to improve the interpretation of the findings and the implications for the future, building on the situation in England and Germany.

The five categories included:

- Countries in which Lyrica was never reimbursed; consequently generic pregabalin is less of an issue for the originator company, see Table 1.
- Countries in which the patent life for Lyrica has been extended, negating the threat from generic pregabalin until all three indications have lost their patent, see Appendix 1.
- Countries in which generic pregabalin is currently not reimbursed and the future situation regarding generic pregabalin is unknown, see Appendix 2.
- Countries in which generic pregabalin is currently not reimbursed; however, the country is likely to follow the example of either the UK and restrict the prescribing of pregabalin for neuropathic pain, alternatively reimburse pregabalin across all indications, see Table 2.
- Countries in which pregabalin is available and reimbursed, see Table 3.

Potential or actual demand-side measures among the health authorities were not broken down into the 'four Es': education, engineering, economics and enforcement, as in our previous paper on generic clopidogrel [52]. This is because pregabalin may not be available and reimbursed across Europe and the other chosen countries.

This information was supplemented with a limited literature search for further information about generics generally, pregabalin and the activities of the originator company, including recent court cases, as well as relevant papers known to the co-authors. A similar methodological approach was used when reviewing health authority activities when generic clopidogrel became available [52].

### Results

The results of the survey revealed that respondents were typically unaware of similar examples to pregabalin and Lyrica in their countries. For example, generic clopidogrel was reimbursed and endorsed by health authority personnel from across Europe despite generic clopidogrel not including all licensed indications at launch [52]. The main exception was Lithuania, see Table 2, with Glivec and generic imatinib.

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The current situation for Lyrica and generic pregabalin among health authorities and health insurance companies across Europe and other selected countries is included in Tables 1–3 as well as Appendices 1 and 2. This also includes additional activities in Scotland.

**Discussion**

In this paper, we have described the situation across Europe following the launch or imminent launch and reimbursement of generic pregabalin. We were not surprised by the activities of the originator company in the UK in view of the current high levels of INN prescribing, no clinical issues with patients being switched between generic pregabalin or Lyrica across indications, and the high sales of Lyrica globally and in the UK [7, 21, 25, 39, 40, 65].

The threat of legal action against physicians taught to prescribe generically is a major concern among health authorities already struggling to fund increased volumes and new high-priced medicines within available budgets [66]. It also raises issues about off-label prescribing generally and pharmacists checking the use of medication with every patient [37]. Moreover, it would seem that this is the first time that an originator company has threatened court cases against physicians in an extended patent use situation. Previous examples can be found in some countries such as Lithuania, see Table 2; however, no coordinated approach has been taken across countries. These concerns are exacerbated if such activities make European markets unattractive for generics companies, thereby reducing potential savings once a product loses its patent. It is also unhelpful to influence physicians to remember to prescribe

different versions of the same molecule for different indications. This could, however, potentially be addressed through increasing use of electronic prescribing support systems. Actions of this nature also impede constructive working relationships between pharmaceutical companies and health service personnel [26].

As seen in Tables 1-3, and Appendices 1 and 2, very different approaches have been taken across countries to the availability of generic pregabalin. In addition to historic approaches taken in Germany, countries such as Czech Republic, Estonia, Republic of Srpska, Bosnia and Herzegovina, and Serbia, see Table 3, are good examples of approaches taken to enhance the prescribing of pregabalin across all indications. The situation in Austria, Poland, and Slovenia will be closely monitored, see Tables 2 and 3, to see if they could also provide examples of potential ways forward to enhance the prescribing of pregabalin across all indications.

Lithuania, Norway and Sweden will also be closely monitored to see whether the originator company will be successful in limiting the prescribing of generic pregabalin in practice to epilepsy and GAD, with Lyrica prescribed and dispensed for neuropathic pain, see Table 2 and Appendix 2. Whether these countries will follow the examples of Bosnia and Herzegovina, Czech Republic, Estonia, Germany (historic), Republic of Srpska Bosnia and Herzegovina, and Serbia, see Table 3, once pregabalin is available and reimbursed remains to be seen.

It is interesting to note the different approaches taken by the originator company to the KVs in Germany initially compared

**Table 1: Health authority situation in countries in which Lyrica was never reimbursed**

**Latvia**

In Latvia, generics of a certain INN are reimbursed for the same indications as the originators, irrespective of the number of indications for the generic versus the originator medicine. A recent example is generic imatinib, which has been reimbursed for all indications since 2013. No patent protection issues are evaluated by the national health service in Latvia when making reimbursement decisions when a generic drug manufacturer has received marketing authorization and is applying for reimbursement. A reference pricing system is in place, and the reference price (which is paid by the state) is the price of the cheapest product. Lyrica is listed but currently not reimbursed in Latvia (100% copayment), including neuropathic pain. Pregabalin Pfizer is centrally registered. Currently, however, no generic pregabalins are available and reimbursed in Latvia. Once available and reimbursed, it is likely that generic pregabalin will be available across all indications similar to the current situation with imatinib.

**New Zealand**

Pregabalin (originator or generic) is currently not funded on the New Zealand Pharmaceutical Schedule in either hospitals or the community for any indications. Lyrica, however, is currently registered for use in New Zealand with indications for neuropathic pain in adults and epilepsy with partial seizures, with or without secondary generalization. Instead, gabapentin is funded on the New Zealand Pharmaceutical Schedule for epilepsy and for neuropathic pain or chronic kidney disease-associated pruritus, with Special Authority restrictions and requirements. PHARMAC (New Zealand’s pharmaceutical funding agency) received an application for pregabalin (Lyrica, Pfizer) for neuropathic pain in 2011 [53]. The advice from the Pharmacology and Therapeutics Committee (PTC the clinical advisory body to PHARMAC) and both its Analgesic and Neurological subcommittees has been that, despite unmet need in the management of neuropathic pain and a clear need for effective treatments, pregabalin has similar effects to gabapentin (albeit faster onset of action), and is unlikely to offer health benefits when gabapentin has failed. The advisory committees to PHARMAC subsequently recommended that pregabalin only be listed for neuropathic pain if it is cost-neutral with respect to gabapentin and subject to the same restrictions; further details are included in the relevant PTAC and subcommittee minutes [54-56]. PHARMAC has very recently received an application for pregabalin for generalized anxiety disorder. As pregabalin is currently not registered in New Zealand for this indication, PHARMAC will not be progressing this application at this point. Pregabalin may be funded in the future in New Zealand if a reasonable price is tendered with pregabalin being included in the 2013-2014 tender. PHARMAC will assess commercial proposals as they arise based on their successful tendering of pharmaceuticals [57].

INN: International Nonproprietary Name.

**Table 2: Health authority situation in countries in which generic pregabalin is currently not reimbursed and the future situation can be predicted**

**Lithuania<sup>a</sup>**

Lyrica is currently reimbursed (about 60% of use is for neuropathic pain and about 40% for epilepsy). The authorities in Lithuania received a letter from the originator company similar to the letter received by Clinical Commissioning Groups in England. As yet, no applications from generic drug manufacturers have been submitted to market generic pregabalin in Lithuania. It is anticipated that, once available, the different products (pregabalin and Lyrica) will be dispensed for different indications (similar to the current situation with Glivec and generic imatinib), potentially enforced through pharmacies.

**The Netherlands<sup>a</sup> [58]**

Lyrica is currently reimbursed and prescribed in The Netherlands for GAD, epilepsy and neuropathic pain. There is currently no generic pregabalin, although pregabalin Krka is registered. The originator company issued letters to the Health Insurance Companies in The Netherlands, including Achmea, which were similar in nature to those issued in the UK, with subsequent follow-up visits from senior procurement officers. Once generics are available and reimbursed, the current preference procurement model for molecules once multiple sources are available will be hindered by the fact that the 2015 preference policy for procurement is closed, only two indications for pregabalin can be procured (epilepsy and GAD) and the perceived financial impact of generic pregabalin is seen as relatively low. Consequently, when two or more generics become available and are reimbursed, generic pregabalin may be a candidate for the IDEA (Preference Pricing Policy) procurement model, as pharmacists should be able to distinguish between the different indications and substitution is not allowed for unapproved indications. Under the IDEA model, there is one fixed price for any 'box of pills', with procurement undertaken by pharmacists to see if any savings can be obtained.

**Norway<sup>a</sup>**

Lyrica is currently reimbursed in Norway for use in epilepsy and palliative care in the terminal stages. Parallel-distributed Lyrica is marketed and substitutable. The indication 'neuropathic pain' is patent protected until July 2017. INN prescribing is possible, but currently limited for these indications. Generic pregabalin with the epilepsy and GAD indications 'are authorized but not yet launched'. Generic pregabalin and Lyrica are currently being assessed by the medical authorities regarding potential substitutability. However, any substitution will not include patent protected indications, i.e. neuropathic pain.

**Sweden<sup>a</sup> [59, 60]<sup>a</sup>**

Generics substitution in general is not allowed by the Swedish Medical Products Agency when epilepsy is a registered indication (parallel-distribution excepted). The indication for prescribing a drug is not available at the pharmacy. Up until August 2015 only parallel-distributed Lyrica and the originator company's own generics preparation were listed as exchangeable. As of September 2015, two separate and mutually exclusive groups of exchangeable drugs exist with Pregabalin Sandoz (lacking the indication neuropathic pain) now included in the new group. Reimbursement in Sweden is in most cases not linked to a specific indication. This was also the case with Lyrica when introduced in 2005. In 2011, reimbursement for GAD and neuropathic pain, but not for epilepsy, was restricted to second-line treatment. In 2014, Lyrica was re-evaluated by TLV (the Dental and Pharmaceutical Benefits Agency – reimbursement agency), owing to lack of compliance to the restrictions. The originator company agreed to lower its price in exchange for continued reimbursement. Pregabalin is typically not recommended in regional formularies. The originator company (in early 2015) wrote to all the Regional Drug and Therapeutic Committees to discuss the situation regarding Lyrica and generic pregabalin. This is ongoing.

**Austria<sup>b</sup>**

At least three pregabalin generics have received marketing authorization in Austria: one is the branded generic from Pfizer (pregabalin Pfizer, authorized on 10 April 2014, centralized procedure, with all three indications, including neuropathic pain). The other two are Pregabalin Krka, authorized on 7 January 2015, and Pregabalin Ratiopharm on 30 March 2015, both for epilepsy and GAD, with the neuropathic pain indication potentially due in the future. More generic pregabalin formulations are anticipated. So far, HVB (reimbursement agency) has received a reimbursement application solely for Pregabalin Krka although others are anticipated. Currently the originator company has not undertaken similar activities to the UK. However, the situation is being monitored. According to the Austrian directive for economic prescribing, physicians are obliged to prescribe the most economical alternative if they are both therapeutically suitable for treatment. As this will be the case with pregabalin generics, prescribing generics for neuropathic pain is envisaged.

**Poland<sup>b</sup>**

Lyrica is reimbursed but only for neuropathic pain in adults caused by cancer, its treatment, or both. The situation is different for gabapentin, which is reimbursed for epilepsy as well as pain for patients with cancer (off label). A reference price system currently exists in Poland, including all generics (branded, accompanied or not by the name of the manufacturer) as well as the originator (brand name). Patients pay a flat rate fee as well as a copayment of 0%, 30%, or 50% depending on the indication. There is also a limit of financing (calculated using defined daily doses – DDDs) based on the cheapest products, with patients paying an additional copayment if they are prescribed a product whose DDD is more expensive than the limit and do not wish it to be substituted. Alternatively, the physician has banned substitution, although there are ongoing initiatives to reduce this [61]. Pharmacists are allowed to substitute in Poland, even if only one indication is approved (recent developments by the Ministry of Health), unless physicians write 'Do not substitute' on the prescription, and this can be clinically justified (must be documented in the patient's notes).

(Continued)

**Table 2: Health authority situation in countries in which generic pregabalin is currently not reimbursed and the future situation can be predicted**  
(Continued)

Currently, no generic pregabalin formulations (including branded generics) are reimbursed in Poland. This could change, and potentially with an increase in the indications including epilepsy and other forms of neuropathic pain, depending on prices offered to the Ministry of Health when it updates the national reimbursement list.

The situation will be closely monitored, especially given the reference price system, pharmacists allowed to substitute, patient pressure to lower costs and the limited reimbursed indications for Lyrica potentially resulting in limited activities by the originator company.

<sup>a</sup>likely to follow the example of the UK; <sup>b</sup>likely to reimburse pregabalin across all indications given current regulations.

GAD: generalized anxiety disorder; HVB: Main Association of Austrian Social Security Institutions; IDEA: Incidence Decay and Exponential Adjustment.

**Table 3: Health authority situation in countries in which pregabalin is currently available or reimbursed across all or some indications****Czech Republic**

Lyrica (the originator), Pregabalin Pfizer, Pragiola, Pregabalin Mylan Pharma, Pregabalin Sandoz and Prelica, are currently available. Pragiola, Pregabalin Mylan Pharma, Pregabalin Sandoz and Prelica are reimbursed for epilepsy, GAD and neuropathic pain, the same indication as Lyrica. No problems have been encountered with setting the reimbursement rate of generic pregabalin in the Czech Republic. Currently, awaiting developments with pregabalin in terms of additional generics formulations, changes in reimbursed prices, or both.

**Estonia**

Pregabalin is 50% reimbursed in Estonia for epilepsy, GAD and neuropathic pain.

Currently, only Pfizer products are reimbursed (generic pregabalin and Lyrica).

In general in Estonia, reimbursement groups are compiled based on INN name, and doctors are obliged to prescribe by INN unless originator name is medically relevant.

**Finland**

Lyrica is reimbursed for epilepsy, GAD and neuropathic pain. All indications are reimbursed (35%). There is 100% reimbursement (special reimbursement category) for patients with epilepsy or other corresponding convulsive states that have partial epileptic seizures, or other forms of refractory epilepsy, where Lyrica could potentially be beneficial (monitored through pharmacies).

The current Pharmaceuticals Pricing Board's decision on reimbursement status for Lyrica is valid through to 31 May 2015.

Pregabalin KRKA was granted similar reimbursement status for epilepsy and GAD on 23 February 2015 with the decision coming into force on 1 April 2015 and valid until the end of the year (no information yet when the product will be launched in Finland with pregabalin currently not reimbursed for neuropathic pain).

Reimbursement for Pregabalin Pfizer has not been applied for.

There are pending marketing authorization applications at Fimea (Finnish Medicines Agency) for pregabalin products by the following applicants: Actavis Group PTC, Orion Pharma, Ratiopharm GmbH and Sigillata Ltd (All applications were delivered in July 2014 – but no further news).

**Iceland**

Generic pregabalin was launched 1 March 2015, as '0-marked' in the medicinal products pricing list, i.e. restricted reimbursement. Reimbursement is only granted after successful individual applications from physicians and subsequently based on the cheapest generic drug.

Conditions for restricted reimbursement

- Epilepsy (ICD-10 G40)
- Peripheral or central neuropathic pain in adults where cheaper medicines, e.g. tricyclic antidepressants (amitriptyline or nortriptyline) or gabapentin, have proved inadequate or are associated with unwanted side effects. In their application, physicians need to specify which medicines have been prescribed and for how long
- Prolonged anxiety disorder in adults where cheaper anxiolytics, i.e. SSRIs and/or SNRIs, have proven ineffective or have unwanted side effects. In their application, physicians need to specify which medicines have been prescribed and for how long

**Republic of Srpska, Bosnia and Herzegovina**

All medicines reimbursed by Republic of Srpska Health Insurance Fund (RS HIF) are by INN.

A reference price system currently exists, in which the reimbursed price for the molecule is the lowest priced product currently on the market, with patients required to cover the difference themselves for a more expensive product.

Generic pregabalin is available in Bosnia and Herzegovina for all three indications, including the treatment of peripheral and central neuropathic pain in adults – Pagamax capsules 25 mg, 75 mg and 150 mg by Nobel Ilaç, Turkey (since June 2014) and Epiiron capsules 75 mg, 150 mg by Bosnalijek, Bosnia and Herzegovina (since February 2015). Pregabalin, however, is currently not reimbursed in the Republic of Srpska (100% copayment).

The application for inclusion of Lyrica on the Positive list was discussed by the HIF Medicines Committee in November 2012, and then rejected. No new application has so far been resubmitted.

Consequently, to date, the originator company has not instigated similar activities in the Republic of Srpska to those undertaken in the UK.

**Serbia**

Lyrica has been on the positive drug list since 2011: Liste A1 with 85% copayment for the indication of neuropathic pain, and on Liste A for indication epilepsy and GAD (lower copayment).

Actavis Zdravlje received marketing authorization from ALIMS from 13 May 2014. From 1 January 2015, generic pregabalin was included on the positive drug list for all indications as the originator (brand name) product, including neuropathic pain.

At the moment of entry, the first generic drug must be priced at least 30% below the originator, setting the reimbursement rate for the molecule.

(Continued)

**Table 3: Health authority situation in countries in which pregabalin is currently available or reimbursed across all or some indications (Continued)**

<p><b>Slovenia</b>                  Lyrica is currently reimbursed by ZZZS (Health Insurance Institute in Slovenia) only for epilepsy and neuropathic pain and not for GAD. Generic pregabalin is on the market in Slovenia and currently in the reimbursement process.                  However, the potential interchangeability of both formulations (originators and generics) has not yet been established by the Agency for Medicinal Products.                  There are regulations in place in Slovenia, however, to establish a therapeutic group (cluster), with the reimbursement level based on the product or molecule with the lowest price with at least one indication matches that of the originator.</p>
<p><b>South Korea</b>                  Currently, 101 generic pregabalin strengths and products are available and reimbursed by the National Health Insurance in Korea: 48 for 75 mg, 1 for 100 mg, 50 for 150 mg and 2 for 300 mg.                  No price difference exists among generics and originators at the same strength.                  In February 2012, 82 generics were listed across the strengths but generics companies were sued for medical use patent infringement by the originator company. Following this, the medical use patent for neuropathic pain is protected until 14 August 2017, with pregabalin generics only available for the treatment of epilepsy.                  Regardless of the patent dispute, the price of Lyrica dropped by 30% in March 2012 and again by 23.5%. It subsequently kept the same price as the generics in February 2013.                  The originator company filed an administrative appeal for the restitution of the drug price in January 2014. The price, however, has not currently changed.</p>
<p><b>Spain (Catalonia)</b>                  Generic pregabalin has been available since January 2015 for epilepsy and GAD.                  The originator company issued a letter in Spain (Catalonia) similar to the letter issued to CCGs in the UK. As a result, the authorities in Catalonia informed physicians that, currently, only Lyrica has the indication for neuropathic pain and should be prescribed for this indication (prescriptions can be monitored through their electronic prescription system including the diagnosis/indication).                  In Spain, however, pregabalin is not an economical issue owing to the reference price system. The reference price (which is paid by the state) is the price of the cheapest product. Consequently to be reimbursed, the originator should reduce its price to the generics price.                  Savings and use of Lyrica have been enhanced by the originator company reducing the price of Lyrica by about 40% from December 2014 to January 2015.</p>
<p><b>UK – Scotland</b>, if different to England [12, 62-64]                  NHS Highland:  <ul style="list-style-type: none"> <li>○ October 2014: physicians urged to increase the generics use versus identified originators including INN prescribing.</li> <li>○ October and November 2014: NHS Highland in their newsletter to physicians suggested that, although, generic pregabalin will only have two indications initially, this should not detract physicians from prescribing generic pregabalin. However, the article was subsequently removed from the newsletter ‘pending discussions’.</li> </ul>                 Activities are ongoing among the other Health Boards in Scotland following a similar letter from the originator company to the CCGs in England. Community Pharmacy Scotland, the equivalent of the English PSNC, issued advice (February 2015) indicating the need for healthcare professionals to stay within licence when the indication is known. They also suggested that, because of the direct to pharmacy distribution model, the originator company will be able to identify changes in the use of Lyrica suggesting that generic pregabalin is being prescribed outside of the current licence and potentially exposing healthcare professionals to the originator company’s patent protection strategy.</p>
<p>ALIMS: Medicines and Medical Devices Agency of Serbia; CCGs: Clinical Commissioning Groups; GAD: general anxiety disorder; INN: International Nonproprietary Names; PSNC: Pharmaceutical Services Negotiating Committee.</p>

with regional health authorities in England and Health Boards in Scotland, see Table 3. This acknowledges adherence to current stipulations of Social Code Book V serving as an example to other countries worried about such developments in the future, although this is now being challenged.

The introduction of reference priced systems with reimbursement typically just covering the costs of the lowest priced molecule is another way forward, given the extent of internal reference pricing across Europe once multiple sources of a product become available [1]. This works best if originator companies drop their prices to compete; alternatively, the situation is pre-empted as seen for instance in Spain, see Table 3. Alternatively, the price of the originator (brand name) is reduced over time despite the protestations of the originator manufacturer, as seen in South Korea, see Table 3. Difficulties could, potentially occur if reimbursement or substitution for one indication is not recommended, which could occur in Sweden for treatments for

epilepsy, see Table 2. This has not currently been a problem in South Korea with multiple pregabalin packs available from different manufacturers, see Table 3. This situation could potentially reduce the attractiveness of the market to generics companies if originator (brand name) manufacturers are happy to drop their prices to those of generics to compete in the knowledge that patients may prefer to stay with the originator if copayments are the same in the absence of any substitution in pharmacies. This is, however, being resisted by the originator company in South Korea, see Table 3.

The developments surrounding Lyrica and generic pregabalin, including potential health authority activities to enhance the prescribing of generic pregabalin, will be closely monitored over the coming months. This will be combined with research on the resultant effect of prescribing and dispensing of pregabalin or Lyrica in practice. The objective will be to provide further guidance to health authorities with their increasing need to maximize

savings from generics or biosimilars once they become available for at least one indication. This is essential to maintain the ideals of comprehensive and equitable healthcare especially in Europe.

### Conclusion

We have documented different approaches to the availability of generic pregabalin, with countries such as Germany historically having measures in place to enhance the prescribing of generics once at least one indication is off patent. This contrasts with countries such as the UK where generic pregabalin can only be prescribed for some but not all indications. This appreciably reduces potential savings from the availability of generics, which is an increasing concern given ever growing pressures on available resources.

### Note from corresponding author

The situation in the UK will now be closely monitored following a recent court judgement post acceptance of the paper overturning the originator company's patent for pregabalin for pain control; although, this is currently being challenged by the company [67].

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**Appendix 1: Health authority situation in countries where the patent life for Lyrica has been extended across indications**

**Australia [1-3]**

There is currently no generic pregabalin in Australia with the originator companies successfully appealing to the Full Federal Court to broaden the scope of an interlocutory injunction restraining the supply of Apotex's pregabalin products. The Apotex challenge to the validity of the epilepsy patent was resolved by consent on confidential terms – the listing for Lyrica for the management of epilepsy on the Pharmaceutical Benefits Scheme (PBS) was rejected in 2005 so actual usage is likely to be very low for this indication. PBS expenditures on pregabalin for neuropathic pain in Australia were anticipated to cost the Australian Government more than AU\$450 million (Euros 320 million) over five years. However, a pricing arrangement has been negotiated between the originator company and the government to reduce the burden for PBS

**France**

Lyrica is currently reimbursed in France, at a rate of 65% since June 2006; the indications are epilepsy/pain central and peripheral/generalized anxiety. LYRICA is not reimbursed for GAD. In France, once the national medicine agency (ANSM) has authorized the drug as a generic, pharmaceutical companies can request reimbursement, which consist of price setting and reimbursement rate setting (the latter with the national health insurance authority – UNCAM). The patent for LYRICA has not expired in France in view of additional protection certificates which allow additional patent protection after launch. Consequently, it is believed unlikely generic pregabalin will be available and reimbursed in France before 2016, perhaps even 2017, although generic pregabalin from Pfizer has received marketing authorization

GAD: generalized anxiety disorder.

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**Appendix 2: Health authority situation in countries where generic pregabalin is currently not reimbursed and future health authority activities are unknown**

**Belgium**

Lyrica was reimbursed by NIHDI (National Institute for Health and Disability Insurance) from 1 February 2006. Currently it is reimbursed in category A as an anti-epileptic drug (0% copayment = Euros 50.13 reimbursed) and in category B (about 25% copayment = Euros 11.80) for diabetes patients with neuropathic pain. There is currently no generic pregabalin reimbursed in Belgium – awaiting developments.

**Croatia**

Lyrica was initially on the basic list of reimbursed medicines, but now on the basic and supplementary lists of the Health Insurance Fund (CHIF)

- On the basic list: LYRICA caps. 56 × 25 mg and caps. 56 × 75 mg for epilepsy.
- On the supplementary list: LYRICA caps. 56 × 150 mg and caps. 56 × 300 mg for epilepsy and GAD but not for neuropathic pain.

Two pregabalin formulations are registered, both from Pfizer, originator and generic, both by centralized proceedings. However, no generic pregabalin is currently reimbursed in Croatia.

**Ireland**

Generic pregabalin is currently not available and reimbursed in Ireland. No information is currently available regarding potential dates when generic pregabalin will be available and reimbursed. However, according to the GaBI (Generics and Biosimilars Initiative) website, six generic pregabalin applications were still being reviewed by EMA as of mid-January 2015.

**Slovakia**

Lyrica has been reimbursed in Slovakia since 1 July 2005 as second-line treatment in patients with epilepsy not responding to agreed first-line therapies and as second-line in patients with neuropathic pain. GAD is not reimbursed. Consumption of all three available strengths' of Lyrica has risen constantly over the years. Prices have reduced by up to 30% in Slovakia from the original starting price. Currently, there are no generic pregabalins available and reimbursed in Slovakia.

GAD: generalized anxiety disorder; SNRI: Serotonin-norepinephrine reuptake inhibitors; SSRI: Selective Serotonin Reuptake Inhibitors.