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Review article

Generic pregabalin; current situation and implications for health authorities, generic and biosimilar manufacturers in the future

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Abstract
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, generics could be legally prescribed for any approved indication once one indication loses its patent.

Aim: To establish the current situation with pregabalin among principally 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 (e.g. Catalonia and South Korea), and current prescribing of pregabablin for all indications (e.g. Serbia and Germany). 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: Health authorities**,** generics, 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 re-directed 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 between the two across a range of products and classes (13-18). In Europe, only generic drugs produced in accordance with the European Medicine's Agency's strict guidelines and definitions (19) are granted marketing authorization.

Well-known and agreed exceptions to generic 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 generic prescribing including medicines to treat epilepsy and prevent organ rejection also exist in Germany and Sweden (6, 24).

A new emerging problem, however, has come to the fore in recent years, concerning the expiry of patents for generic drugs 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 pregablin for the treatment of 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 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 pregablin 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 registered for this indication (43). In addition, there have been concerns with the methodological limitation of some of the studies of pregabalin in neuropathic pain(32-34). 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 (35). However, there are increasing concerns with the implications of the activities of second use patents with Lyrica (26, 36).

In this paper, historical developments in the UK and Germany relating to this case are examined. Personnel from regional and national health authorities from principally across Europe, and advisors 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, International Nonproprietary 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 drugs is prescribed (7, 20, 21, 37).

The UK Medicines Agency recently issued advice on which epilepsy drugs to prescribe by brand name (originator) and which by INN (38). Pregabalin was considered suitable for INN prescribing (38), 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 November 2014 pointing out that generics of pregabalin were expected to be approved only for GAD and epilepsy indications only, and that the prescribing of generic pregabalin for neuropathic pain would 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 generic 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, 39). 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 (39, 40).

The actions of the originator company are unsurprising. In 2013, global sales of Lyrica generated $4.6 billion for the company (39). 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 (39). In 2014, sales of Lyrica were GB£250million (US$390million) (26).The potential loss in revenue therefore, would hugely impact company sales - estimated to be £GB 220million per year (US$340million) across all indications assuming high INN prescribing rates and generic prices rapidly falling by 90% of the price of Lyrica (7, 41) .

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 Practice Committee of the BMA, and the National Health Service (26, 36, 42-44). For instance, 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' (43).* 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 producers would write to CCGs to ensure they were aware that the generic 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' (42).

This situation in the UK has important future implications for generic and biosimilar 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 to court in an attempt to conserve Lyrica sales for neuropathic pain (10 April 2015) (45). The legal battle is still ongoing. The originator company's previous strategy to promote Lyrica was to communicate directly with physicians or via KV's (regional doctors´ associations) by letter, making it clear that Lyrica was the only pregabalin licensed for neuropathic pain. However, these communications were largely dismissed by KV's because the focus was on legal rather than medical issues, and the KV's continued to advise physicians to reach targets of generic prescribing of at least 85%. In addition, the

Social Code Book V (SGB V), which is decisive for Sickness Funds (German payers), stated in paragraph 129 that generic substitution is possible wherever at least one indication matches (46-49).

The contrast between the situation 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, principally 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 from principally 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 in England and Germany, and is in line with current recommendations for conducting cross-national research projects (50). The aim was to maximixe 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 pregablin 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 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 Western, Central and Eastern Europe to ensure legitimacy with the findings. Personnel from regions in the Netherlands, Sweden and UK were also included, as healthcare budgets in these regions 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 one author (BBG). 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 (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 (Appendix 1).
- Countries in which generic pregabalin is currently not reimbursed and the future situation is currently unknown (Appendix 2).

- Countries in which generic pregabalin is currently not reimbursed; however, the country is likely to follow the example of either UK and restrict the prescribing of pregabalin for neuropathic pain, alternatively reimburse pregabalin across all indications (Table 2) .
- Countries in which pregabalin is available and reimbursed (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 (51). 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 (51).

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 (51). The main exception was Lithuania (Table 2) with Glivec and generic imatinibum.

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 Appendix A1 and A2. This also includes additional activities in Scotland.

Table 1 – Countries in which LYRICA was never reimbursed.

Country	Health authority situation
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. A recent example is generic imatinibum, 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 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% co-pay), 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 imatinibum.
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 (52). The advice from the Pharmacology and Therapeutics Committee (PTAC, 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 (53-55). • 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. • Pegabalin 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 (56).

Table 2: Countries in which generic pregabalin is currently not reimbursed and the future situation can be predicted (likely to follow the example of the UK[a] or likely to reimburse pregabalin across all indications given current regulations[b]).

Country	Health authority situation
Lithuania[a]	• 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 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 imatinibum), potentially enforced through pharmacies.
Netherlands[a] (57)	• 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 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 they any savings can be obtained.
Norway[a]	• 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[a] (58, 59)[a]	• So far only parallel distributed Lyrica and Pfizer´s own generic preparation are on the list of exchangeable generic drugs. • The Swedish reimbursement system is in most cases not linked to a specific indication, and this was also the case with Lyrica when it was introduced in 2005. • Since Lyrica is registered for epilepsy, generic substitution most probably will be discouraged via the Swedish Medicines Product Agency (as with all products for epilepsy in Sweden), with a revised list of substitutable pharmaceuticals imminent. In addition, the Swedish system doesn't allow information about the prescribing indication to be communicated to the pharmacy and used in decisions about reimbursement • In 2014, Lyrica was again re-evaluated by the TLV (Swedish Reimbursement Agency) owing to concerns with compliance. As a result, the originator company agreed to lower its price in exchange for TLV making no changes to LYRICA's reimbursement status. • The originator company has written to the County Councils' (Region) Drug and Therapeutic Committees (DTCs) requesting meetings to discuss the situation regarding LYRICA and generic pregabalin (January and February 2015). This is being monitored especially with pregabalin (Lyrica) typically not recommended in

	regional formularies.
Austria[b]	• 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[b]	• 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 co-payment 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 co-payment 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. • 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). • Currently, no generic pregabalin formulations (included 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.

GAD, Generalized anxiety disorder.

Table 3: Countries in which pregabalin is currently available or reimbursed across all or some indications.

Country	Health authority situation
Czech Republic	• Both Lyrica (the originator) and Pregabalin Pfizer (registered with a generic reference to the original registration, the marketing authorization holder is the same) are currently available. • Out of these two, only one (Lyrica) is currently reimbursed (epilepsy, GAD and neuropathic pain); however, this is now subject to an ongoing reassessment of its reimbursement price. • Currently awaiting developments with Lyrica and generic pregabalin in the Czech Republic.
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).
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 Epiron 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% co-payment). • 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 re-submitted. • 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% co-payment for the indication of neuropathic pain, and on Liste A for indication epilepsy and GAD (lower co-payment). • 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 must be priced at least 30% below the originator, setting the reimbursement rate for the molecule.
Slovenia	• Lyrica is currently reimbursed by ZZZS (Health Insurance Agency 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 once at least one indication matches that of the originator.
South Korea	• Currently, 101 generic pregabalin strengths and products are available and reimbursed by the National Health Insurance in Korea: 48 for 75 mg, one for 100 mg, 50 for 150 mg and two 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 generic 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 Aug 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
Spain (Catalonia)	• 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 generic price. • Savings and use of yrica have been enhanced by the originator company reducing the price of LYRICA by about 40% from December 2014 to January 2015.
UK – Scotland (if different to England – Box 1) (12, 60-62)	• NHS Highland: o October 2014: physicians urged to increase the generic use versus identified originators including INN prescribing. o 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'. • 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.

GAD, General anxiety disorder; INN, International nonproprietary names.

Discussion

In this paper, we have described the situation across Europe following the launch or imminent launch and reimbursement of 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, 38, 39, 63). The originator company had also recently experienced considerable loss of revenue when both atorvastatin and sildenafil lost their patents.

The threat of legal action against physicians taught to prescribe economically is a major concern among health authorities already struggling to fund increased volumes and new high-priced medicines within available budgets (64). It also raises issues about off-label prescribing generally and pharmacists checking the use of medication with every patient (36). 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 (Table 2); however, no co-ordinated approach has been taken across countries. These concerns are exacerbated if such activities make European markets unattractive for generic companies, thereby reducing potential savings once a product loses its patent. It is also unhelpful to make physicians 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 Estonia, Republic of Srpska, Bosnia and Herzegovina, and Serbia (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 (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 pregabalin in practice to epilepsy and GAD, with Lyrica prescribed and dispensed for neuropathic pain (Tables 2 and Appendix 2). Whether these countries will follow the examples of Estonia, Germany (historic), Republic of Srpska, Bosnia and Herzegovina, and Serbia (Table 3) once pregabalin is available and reimbursed remains to be seen. The outcome of potential marketing authorization and reimbursement of additional pregabalins in the Czech Republic, in addition to Pfizer's own generic pregabalin, will also be monitored given current uncertainties (Table 3).

It is interesting to note the different approaches taken by the originator company to the KVs in Germany initially compared with regional health authorities in England and Health Boards in Scotland (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 (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 (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 (Table 2). This has not currently been a problem in South Korea with multiple pregabalin packs available from different manufacturers (Table 3). This situation could potentially reduce the attractiveness of the market to generic 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 co-payments are the same in the absence of any substitution in pharmacies. This is, however, being resisted by the originator company in South Korea (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.

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