HEAD OF MEDICINES MANAGEMENT v PFIZER

Gabapentin Patient Alert

A medicines management pharmacist complained about a gabapentin patient alert issued by Pfizer. Gabapentin was available generically and marketed by Pfizer as Neurontin. Pfizer also marketed Lyrica (pregabalin). Both Neurontin and Lyrica were indicated for use in neuropathic pain and in epilepsy.

The complainant noted the alert which read, 'Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. *Supported by Pfizer.*'. The alert was activated on some community pharmacy 'Patient Medication Records' (PMR) systems when gabapentin was entered into the system.

The complainant alleged that this activity was disguised promotion and did not maintain high standards. If the Authority agreed, then the complainant also alleged that the activity brought the industry into disrepute.

The complainant submitted that the most likely alternative to gabapentin was pregabalin. The alert suggested that the alternative medicine would have fewer side effects and a safer prescribing profile. However Public Health England had recently alerted health professionals that both gabapentin and pregabalin could to lead to dependence and that they might be misused or diverted. The complainant stated that implying that pregabalin was likely to be a better alternative could be misleading. In addition, the statement directed pharmacists and patients to an alternative without encouraging them to report adverse events through the Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card system. Thus the complainant alleged that the objective of the alert was promotional rather than patient support.

The detailed response from Pfizer is given below and refers to seven different patient alerts for amitriptyline and gabapentin.

The Panel considered that the provision of high quality patient care was an important aim. However it was concerned that Pfizer considered that pharmacists needed to be given the seven patient alerts to support their discussions with patients. The advice regarding adverse events and what to do if symptoms were not controlled was likely to be relevant for all medicines not just those used to treat neuropathic pain. The Panel noted that the patient alerts which referred to adverse events did not remind pharmacists to report them. The Panel also noted that the patient alerts appeared irrespective of whether amitriptyline or gabapentin had been prescribed for neuropathic pain or something else. The patient alerts appeared on the dispensing terminal and not on the patient medication records.

The Panel noted Pfizer's submission that the National Institute for Health and Care Excellence (NICE) recognised that there was considerable variation in how medicines for neuropathic pain were initiated, the dosages used and the order in which they were introduced. NICE noted that for the treatment of all neuropathic pain (except trigeminal neuralgia), initial treatment should be a choice of amitriptyline, duloxetine, gabapentin or pregabalin. If initial treatment was not effective/not tolerated, then one of the three remaining medicines should be offered with subsequent switches being considered if the second or third medicines tried were also not effective/not tolerated. Pfizer marketed two of the four medicines recommended for initial treatment.

The Panel noted that gabapentin and amitriptyline were the most commonly used first-line treatments for phantom limb pain or painful diabetic neuropathy (Hall *et al* 2013). Pfizer submitted that 61% of gabapentin prescriptions were for pain and that pregabalin was much less frequently prescribed. The Panel noted that given the NICE treatment guidelines, if a patient had initially been unsuccessfully treated with amitriptyline, then two of the other three medicines which should be tried were Pfizer's (gabapentin and pregabalin). However given that amitriptyline and gabapentin were the two most widely prescribed medicines for neuropathic pain, a patient who had failed initially with amitriptyline was likely to be switched to gabapentin and *vice versa*.

The Panel noted that although the seven patient alerts were to be used in rotation, triggered by prescriptions for gabapentin or amitriptyline, the complainant had complained about the one which read: 'Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. *Supported by Pfizer.*' The Panel noted the NICE guidelines and that a patient who failed on gabapentin would not necessarily be switched to pregabalin, there were two additional medicines the patient could try depending where they were on the treatment pathway. Although a switch to pregabalin was possible, the Panel did not have evidence before it to show that, as suggested by the complainant, it was the most likely alternative. The Panel noted Pfizer's submission that health professionals did not differentiate pregabalin from gabapentin as their mechanisms of action were similar. The Panel did not consider that the patient alert at issue for gabapentin was disguised promotion for pregabalin as alleged and it ruled no breach. The Panel thus did not consider that the text cited by the complainant implied that pregabalin was likely to be a better alternative to gabapentin or that it suggested that, compared with gabapentin, pregabalin had fewer side effects and a

safer prescribing profile. No breaches of the Code were ruled.

The Panel noted its rulings above and considered that there was no evidence to show that high standards had not been maintained. The Panel did not consider that failing to refer to the reporting of adverse events in the patient alerts in itself meant that high standards had not been maintained. However if it was considered helpful to remind pharmacists about certain elements to support their interactions with patients, then it would have been helpful to also include a reference to the MHRA yellow card scheme. Pfizer had not specifically responded on this point. Nonetheless, the Panel considered that there had been no breaches of the Code including Clause 2.

A head of primary care support and medicines management at a clinical commissioning group (CCG), complained on behalf of that CCG and colleagues from other CCGs, about the activities of Pfizer Limited. The material at issue was a patient alert about gabapentin. Gabapentin was widely available generically and marketed by Pfizer as Neurontin. Pfizer also marketed Lyrica (pregabalin). Both Neurontin and Lyrica were indicated for use in the treatment of epilepsy and neuropathic pain.

COMPLAINT

The complainant stated that the alert was activated on some community pharmacy 'Patient Medication Records' (PMR) systems, triggered when gabapentin was entered into the system..

The patient alert read:

> 'Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. *Supported by Pfizer*.'

The complainant alleged that this activity contravened the Code in relation to disguised promotion, Clause 12.1 that promotional material and activities must not be disguised and Clause 9.1 that high standards of compliance to the Code must be maintained at all times. If the Authority agreed with this, the complainant also alleged a breach of Clause 2, bringing the industry into disrepute.

Clinically, the most likely alternative to gabapentin was another Pfizer medicine, pregabalin, a medicine licensed for use in epilepsy, generalised anxiety disorder and neuropathic pain. The medicines had a very similar structure, acting via the alpha-2-delta subunit of voltage-gated calcium channels.

The alert suggested that the alternative medicine would have fewer side effects and implied a safer prescribing profile. Public Health England had recently alerted health professionals that both gabapentin and pregabalin had the potential to lead to dependence and that they might be misused or diverted.

The complainant stated that implying that pregabalin was likely to be a better alternative could be misleading. In addition, the statement directed pharmacists and patients to an alternative without encouraging/directing them to report their adverse event through the Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card system. Thus the complainant alleged that the alert was a promotional message rather than a supportive statement for patients.

When writing to Pfizer, the Authority asked it to consider the clauses cited by the complainant (2, 9.1 and 12.1) and also Clause 7.2 in relation to the alleged misleading implication that pregabalin was likely to be a better alternative and Clause 7.9 in relation to the alleged suggestion that pregabalin would have fewer side effects and a safer prescribing profile including the comments about dependency and misuse.

RESPONSE

Pfizer submitted that, despite better diagnosis and advances in treatments, the management of neuropathic pain remained very challenging because of the heterogeneity of its aetiologies, symptoms and underlying mechanism. Patients with neuropathic pain could suffer severe pain which could have a significant impact on their quality of life. No single treatment worked in every patient or pain state, and satisfaction with therapy was relatively low in patients with neuropathic pain (Dworkin *et al*, 2010). In randomised clinical trials of medicines for neuropathic pain, many patients did not experience clinically meaningful pain relief and, in addition, frequently experienced burdensome side effects and so might not be able to tolerate their treatment. These results from clinical trials were consistent with several studies of neuropathic pain in the community (Dworkin *et al*).

Pfizer stated that the National Institute for Health and Care Excellence (NICE) Clinical Guideline 173 [Neuropathic pain – pharmacological management] recognised that there was considerable variation in how medicines were initiated, the dosages used and the order in which they were introduced, whether therapeutic doses were achieved and whether there was correct sequencing of therapeutic classes. It was further noted that these factors might lead to inadequate pain control with considerable morbidity. There was a recognition that, 'untreated, pain became entrenched and more difficult to treat. The consequences of long-term pain had a serious impact on both patients and society' (Chief Medical Officer report 2009). A general principle of pain management, as recognised by The British Pain Society/Map of Medicine neuropathic pain guidelines, was the need to reduce delays in optimising pain management for patients.

Pfizer stated that the supplier of the particular PMR system at issue supported patients at the point of dispensing medicines within a pharmacy. The company was committed to improve patients' health and prevent unnecessary suffering by helping patients understand their medicines better. With this aim the supplier supported better adherence to medicines and optimisation of care. The company supported pharmacists and patients and since setting

up it had worked with most of the top 20 life sciences companies in the UK to support approximately 50% of UK pharmacies and 42,000 pharmacies across Europe.

Pfizer submitted that pharmacists routinely gave patient information when they collected their prescription. The PMR supplier was able to provide additional helpful information on the electronic dispensing system to support the discussion with patients. Dispensing the prescribed treatment(s) triggered the information to appear in the electronic dispensing system. The objective of the information was to optimise patient care. The pharmacy intervention was intended to identify patients whose care might not be optimised and to advise them to consult their doctor to see if they might be suitable for alternative treatment options. Alternative treatment options were never named, and could be pharmacological or non-pharmacological.

Given the patient-focussed objectives of the PMR supplier, Pfizer had engaged with it to create information for pharmacists to give to patients whey they dispensed gabapentin and amitriptyline, the most commonly prescribed medicines for neuropathic pain (Hall *et al* 2013).

Given the patient, healthcare and societal challenges as set out above in managing neuropathic pain, the aim of the patient information was to:

- Support pharmacists when they counselled patients to identify if they had experienced inadequate pain relief or side effects from their treatment, and if so to advise the patient to consult their doctor as other treatment options, pharmacological or non-pharmacological, might be suitable for them. The counselling supported patients to make informed choices and manage their condition with support from their health professional.

- Support better management of neuropathic pain in primary care. There was an accepted burden associated with outpatient and pain clinic referrals into secondary care and this could be reduced, where appropriate, with better management of pain in primary care.

The information texts for patients were detailed below, however the complaint specifically related to number 2 (ref NEP0134b). The PMR supplier conducted due diligence with feedback from the PMCPA which twice supported the view that provided the text did not promote a medicine, the information for patients could be regarded as non-promotional. These were certified as non-promotional items (refs NEP0134a/b/c and NEP0227a/b/c/d).

1 Remind your patient that if they are still having pain and/or experience side effects, they should return to their doctor, as alternative treatments are available. Supported by Pfizer Ltd (ref NEP0134a)

2 Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. Supported by Pfizer Ltd (ref NEP0134b)

3 Remind your patient that if they are not getting adequate pain relief whilst taking gabapentin they should return to their doctor, as alternative treatments are available. Supported by Pfizer Ltd (ref NEP0134c)

4 Research shows 38% of people taking amitriptyline for neuropathic pain achieve pain relief. If your patient isn't getting adequate pain relief, advise them to discuss with their doctor as there are other treatments available. Supported by Pfizer Ltd (ref NEP0227a)

5 Inform your patient that some people experience side effects whilst taking amitriptyline. If this is the case, they should discuss with their doctor as alternative treatments are available. Supported by Pfizer (ref NEP0227b)

6 NICE recommends amitriptyline as an initial treatment option for neuropathic pain but many patients may remain in pain. If your patient is still symptomatic, they should speak to their doctor – other treatments are also recommended. Supported by Pfizer (ref NEP0227c)

7 64% of patients on amitriptyline experience at least one adverse event. These may pass; however, if they continue, advise your patients to discuss with their doctor. There are alternatives available. Supported by Pfizer (ref NEP0227d).

The information did not appear on the community pharmacy patient medication records. It appeared on the electronic dispensing system when the medicine was dispensed to enable the information to be provided to the patient by the pharmacist.

Pfizer had not paid for its publication on the patient medication records. The service was not on the patient medication record. It was triggered at the point of dispensing within the dispensing terminal via the PMR desktop application, to enable patient support information to be provided to the patient by the pharmacist. Pfizer had paid for the publication on the dispensing terminal via its desktop application within PMR supplier's pharmacies estate.

Essentially, the alerts prompted the pharmacist to consider the discussion points as part of the counselling normally provided to patients when they received their medicines. There was no additional material provided to the pharmacist.

Pfizer stated that the patient information was certified as non-promotional text and Pfizer ensured that the information did not promote any medicine. Pfizer had been very clear to state that 'alternative treatments were available'. Alternative treatments encompassed a wide number of treatment options, both pharmacological and non-pharmacological (ie pain management programmes, complementary and alternative treatments, exercise, transcutaneous electrical nerve stimulation, percutaneous electrical nerve stimulation, graded motor imagery, cognitive behavioural therapy or supportive psychotherapy, based on the bio-psychosocial model of pain). Indeed, the National Pain Audit showed that 44% of treatment received from NHS pain services was non-

pharmacotherapy (National Pain Audit, 2010-2012). Pfizer therefore did not accept that this information for patients was disguised promotion for pregabalin or any medicine, and as such was not in breach of Clause 12.1.

Pfizer noted the complainant's following points:

- 'Clinically the most likely alternative to gabapentin was another Pfizer medicine, pregabalin'
- 'The alert suggested that the alternative medicine would have fewer side effects and implied a safer prescribing profile'
- 'Public Health England had recently alerted health professionals that both gabapentin and pregabalin had the potential to lead to dependence and that they might be misused or diverted'.
- 'Implying that pregabalin was likely to be a better alternative could be misleading'.

Pfizer disagreed that 'alternative treatments' most likely implied pregabalin and referred to its comments above regarding the wide number of treatment options, both pharmacological and non-pharmacological encompassed in 'alternative treatments'.

There was no suggestion that patients would have fewer side effects or do better with any other options. The text simply advised patients to see their doctor if they experienced side effects as alternative treatment options might be suitable for them. The British Pain Society/Map of Medicine neuropathic pain guidelines highlighted the holistic management of neuropathic pain (pharmacological and/or non-pharmacological) delivered in non-specialist care, and the need for optimal pain management. Many patients had to try many options, both pharmacological and non-pharmacological, before they found a suitable option. This would be in line with standard clinical practice. As there were no promotional claims in this patient information Pfizer denied breaching Clauses 7.2 or 7.9.

Pfizer submitted the programme had undergone due diligence within the company; it had involved medical, legal and compliance colleagues. Pfizer again noted that advice about this type of programme had been sought from the PMCPA. The feedback supported Pfizer's assessment that this was a non-promotional programme which provided information to patients to support their care. Pfizer ensured that there was no promotion or disguised promotion of any medicines. Pfizer was dedicated and committed to maintaining the highest standards of compliance and it believed that high standards had been maintained at all times throughout this patient information programme. Pfizer did not accept that the patient information provided breached Clause 9.1.

Pfizer submitted that as the patient information provided did not represent disguised promotion of pregabalin or any medicine and that high standards of compliance had been maintained at all times, it denied that it had brought the industry into disrepute or breached Clause 2.

In summary, Pfizer reiterated that pharmacological management of neuropathic pain was recognised as challenging. Many patients did not achieve clinically meaningful pain relief and, in addition, might experience burdensome side effects and so were often unable to continue their treatment.

The programme's objective was to optimise the care of patients with neuropathic pain by providing information for them to be delivered by pharmacists at the point of dispensing. This supported the pharmacist when he/she counselled patients to identify if they had experienced inadequate pain relief or side effects and if so, to advise the patient to consult their doctor. Alternative treatment options could include other pharmacotherapies and/or a wide choice of non-pharmacotherapies which were commonplace in pain management. There was no disguised promotion of pregabalin or any medicine or therapy. There were no promotional claims or comparisons and high standards had been maintained throughout. Pfizer thus did not accept that the patient information text breached Clauses 12.1, 7.2, 7.9, 9.1 or 2.

In response to a request for further information, Pfizer submitted that although gabapentin 900-3,600mg/day was licensed for both peripheral neuropathic pain and epilepsy, the vast majority of its use was in pain (61% pain, 1% epilepsy, 39% other) (Ref IMS). Pfizer reiterated that patients were not always optimally treated for neuropathic pain and the aim of the programme was to help address this. The company had focused on gabapentin and amitriptyline as these were the most commonly used treatments for neuropathic pain.

Pfizer noted that the alerts were triggered by the medicine being presented, irrespective of indication. As UK prescriptions did not include the indication, the computer system would not be able to identify what the prescription was for.

Pfizer stated that it did not have the data to show what proportion of patients with peripheral neuropathic pain were likely to be switched to pregabalin if they could not tolerate gabapentin. However, from experience, many health professionals did not differentiate pregabalin from gabapentin as their mechanisms of action were similar. Similarly, the company did not have the data to show what proportion of patients with epilepsy were likely to be switched to pregabalin if they could not tolerate gabapentin.

Pfizer noted that the alerts were rotated on a monthly basis such that one month it would be alert 1, the next alert 2 and so on, there was no prioritisation or weighting given to a particular message.

Pfizer submitted that the alerts did not refer to pharmacological and non-pharmacological treatments, because the PMR desktop application only allowed a maximum of 254 characters and spaces in each alert. Thus due to the character limitation 'treatments' was an appropriate term as it encompassed a wide range of treatment options (pharmacological and non-pharmacological).

Pfizer stated that its objective with this programme was to support patient care by helping the pharmacist to engage the patient in dialogue about their treatment. The patient alert was triggered when either gabapentin or amitriptyline were dispensed as these were the two most commonly used treatments for neuropathic pain. The alerts were not triggered when pregabalin or duloxetine were dispensed as these were much less frequently prescribed.

The alerts prompted the pharmacist to discuss the patient's treatment with them in the course of their natural duties. This was non-promotional material hence the adverse events reporting statement required for promotional material was not required. The alert itself was not directed to the patient nor intended to be shown to the patient so 'reporting of side effects' wording for the patient was not included.

Pfizer stated that the above further supported its position that the patient information text was not in breach of the Code.

PANEL RULING

The Panel noted Pfizer's submission that the Authority had been asked for its view on a patient alert programme and that feedback from the Authority had supported the view that the activity was non-promotional. The Panel noted, however, that when the Authority was asked for advice about materials or activities under the Code it could only give informal guidance based upon its interpretation of the Code and, where available, the outcome of past cases. The Authority could not approve such materials or activities and that if a complaint were to be received about a matter upon which advice had been sought, it would have to be considered in the usual way and on its own particular merits.

The Panel considered that the provision of high quality patient care was an important aim. However it was concerned that Pfizer considered that pharmacists appeared to need to be given the information in the seven patient alerts to support their discussions with patients. The advice regarding adverse events and what to do if symptoms were not controlled was likely to be relevant for all medicines not just those used to treat neuropathic pain. The Panel noted that the patient alerts which referred to adverse events did not remind pharmacists of the need to report them. The Panel also noted that the patient alerts would appear irrespective of whether the patient was prescribed amitriptyline or gabapentin for neuropathic pain or some other indication. The patient alerts appeared on the dispensing terminal and not on the patient medication records.

The Panel noted Pfizer's submission that NICE recognised that there was considerable variation in how pharmacological treatment for neuropathic pain was initiated, the dosages used and the order in which medicines were introduced, whether therapeutic doses were achieved and whether there was correct sequencing of therapeutic classes (NICE CG173). The NICE clinical guideline cited noted that for the treatment of all neuropathic pain (except trigeminal neuralgia), initial treatment should be a choice of amitriptyline, duloxetine, gabapentin or pregabalin. If initial treatment was not effective or was not tolerated, then one of the three remaining medicines should be offered with subsequent switches being considered if the second or third medicines tried were also not effective or not tolerated. Pfizer marketed two out of the four medicines recommended for initial treatment.

The Panel noted that gabapentin and amitriptyline were the most commonly used first-line treatments for patients with phantom limb pain or painful diabetic neuropathy (Hall *et al*). Pfizer submitted that 61% of gabapentin prescriptions were for its use in pain and that pregabalin was much less frequently prescribed. The Panel noted that given the treatment guideline from NICE, if a patient had initially been unsuccessfully treated with amitriptyline, then two of the other three medicines which should be tried were Pfizer's (gabapentin and pregabalin). In the Panel's view given that amitriptyline and gabapentin were the two most widely prescribed medicines for neuropathic pain, a patient who had failed on initial treatment with amitriptyline was likely to be switched to gabapentin and vice versa.

The Panel noted that although Pfizer had produced seven patient alerts to be used in rotation, triggered by prescriptions for gabapentin or amitriptyline, the complainant had complained about the one which read: 'Remind your patient that they may experience side effects whilst taking gabapentin. If this is the case they should return to their doctor as alternative treatments are available. Supported by Pfizer.' The Panel noted the NICE treatment guidelines above and that a patient who failed on gabapentin would not necessarily be switched to pregabalin, there were possibly two additional medicines the patient could try depending where they were on the treatment pathway. Although a switch to pregabalin was a possibility the Panel did not have evidence before it to show that, as suggested by the complainant, clinically the most likely alternative to gabapentin was pregabalin. The Panel noted Pfizer's submission that health professionals did not differentiate pregabalin from gabapentin as their mechanisms of action were similar. The Panel did not consider that the patient alert at issue for gabapentin was disguised promotion for pregabalin as alleged and it ruled no breach of Clause 12.1. Given that the Panel did not consider that the patient alert promoted pregabalin, it also did not consider that the text cited by the complainant implied that pregabalin was likely to be a better alternative to gabapentin as alleged. No breach of Clause 7.2 was ruled. Similarly, the Panel did not consider that the patient alert suggested that compared with gabapentin, pregabalin had fewer side effects and a safer prescribing profile. No breach of Clause 7.9 was ruled.

The Panel noted its rulings above and considered that there was no evidence to show that high standards had not been maintained. The Panel did not consider that failing to refer to the reporting of adverse events in the patient alerts in itself meant that high standards had not been maintained. However if it was considered helpful to remind

pharmacists about certain elements to support their interactions with patients, then it would have been helpful to also include a reference to the MHRA yellow card scheme. Pfizer had not specifically responded on this point. Nonetheless, the Panel considered that there had been no breach of Clause 9.1 and ruled accordingly.

Given the rulings above, the Panel ruled no breach of Clause 2 of the Code.

Complaint received **11 June 2015**

Case completed **14 August 2015**