PATIENT v AMGEN and GLAXOSMITHKLINE

Patient information on Prolia

A patient who had been prescribed Prolia (denusumab) complained about the information which Amgen UK had supplied about the medicine. Prolia was indicated, *inter alia*, for the treatment of osteoporosis in postmenopausal women at increased risk of fractures. The matter was subsequently taken up with GlaxoSmithKline UK which co-promoted Prolia.

The complainant explained that in August 2012, she received an injection of Prolia at a local hospital. Before agreeing to treatment she had been told that the only side effects were those listed in the leaflet issued by a national patient support group. The complainant submitted that this leaflet was inaccurate.

Upon receiving treatment the complainant was given a German package leaflet and so she could not identify any side effects that were not listed in the leaflet from the national patient support group. The complainant submitted that the German leaflet implied that she was illegally administered a medicine that was not licensed for use in the UK and was intended for only countries in which the side effects were explained. The complainant raised the matter with both her consultant and with Amgen in 2012 and received no acknowledgement from Amgen.

The complainant stated that within 3-6 weeks, she experienced unexpected side effects, not listed in pre-treatment information supplied by Amgen, in that she had cracks at the side of her mouth and severe mouth and tongue ulcers. The complainant contacted the national patient support group which told her that this was a side effect of Prolia and that the medicine had a yellow card marker. The complainant submitted that she was never told that Prolia was still on trial and that she had not been given enough information upon which to make an informed decision to start treatment.

The complainant and her consultant had both contacted Amgen in 2013 but the complainant submitted that the company was not helpful. Amgen denied all knowledge of mouth ulceration and only referred to osteonecrosis of the jaw. The booklet provided by Amgen after Prolia had been administered clearly listed non-healing sores of the mouth as a 'rare side effect'.

The complainant considered that, without her knowledge, she had been included in a trial. If she had known that Prolia had a 'yellow marker' she would not have agreed to treatment.

The complainant submitted further information and copies of correspondence between her consultant and Amgen and alleged that Amgen appeared to be withholding details of mouth ulceration in the UK in order to obtain a licence for Prolia. The company appeared to state that it did not need to list all side effects under UK regulations and so the information had been withheld. In the complainant's view Amgen appeared to be ignoring its 'duty of care' to all patients. The complainant noted that mouth ulceration was referred to in information given to patients in other countries and she requested a full investigation into the conditions relating to the use of Prolia in the UK.

The detailed responses from GlaxoSmithKline and Amgen are given below.

The Panel noted that the complainant was a patient who considered that she had experienced an adverse event as a result of the administration of Prolia. The Panel noted that invariably such individuals were only moved to complain when they felt strongly about a matter. The Panel noted that whilst the complainant raised a number of matters it could only consider those which fell within the scope of the Code. Patient safety was extremely important. It was not clear whether the patient had reported the side effect under the yellow card scheme but she had discussed the matter with various health professionals and been in contact with Amgen. The relevant procedures at Amgen should have ensured that the data was dealt with appropriately.

The Panel noted the relationship between Amgen and GlaxoSmithKline in relation to the promotion of Prolia. It further noted GlaxoSmithKline's submission that its role was limited to the patient support booklet and the Panel considered that aspect of the complaint in relation to both companies.

In the complaint against Amgen the complainant's general concern was about the alleged failure to provide information about side effects prior to the administration of Prolia and the failure to provide appropriate information in subsequent correspondence.

The Panel noted that the complainant's physician was responsible for her clinical care and associated matters. Pharmaceutical companies were only responsible under the Code for matters which came within its scope including the provision of material for patients. Amgen had provided information to the complainant and to the complainant's physician.

The Panel noted Amgen's submission that it had not been involved in any patient materials used by the national patient support group.

The Panel noted the complainant's concern that she had been provided with a foreign language patient leaflet after the medicine had been administered.

The Panel noted Amgen's explanation; the Prolia box had two patient leaflets, one in German and one in English. The health professional who administered the product read the English version, handing the unopened German version to the complainant. According to Amgen the hospital had apologised to the complainant about this matter. That the health professional had failed to give the complainant the English leaflet provided was not Amgen's responsibility under the Code. The Panel considered that this matter was most unfortunate and had caused the complainant distress. Nonetheless, the Panel considered that both the content of non-promotional package leaflets and the provision of the wrong version to the complainant were not matters that Amgen was responsible for under the Code. The Panel ruled no breach of the Code as both matters were outside the scope of the Code.

The complainant appeared to be under the misapprehension that she was on a clinical trial sponsored by Amgen. That was not so. Amgen submitted that it had not supported any trials at the hospital and the complainant's physician had confirmed that the administration of Prolia was not part of any trial. The product had a marketing authorization. It appeared from the complaint that this misunderstanding might have arisen when the complainant was advised by a patient organisation that there was a 'yellow card marker on Prolia' by which the Panel assumed that the complainant was referring to the Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card scheme for reporting suspected adverse events. The Panel noted that the yellow card scheme applied to, *inter alia*, all medicines and vaccines irrespective of how long they had been on the market. The Panel noted Amgen's submission that all Prolia promotional materials included the required statement regarding how adverse events should be reported. The Panel noted that the complainant bore the burden of proving her complaint on the balance of probabilities. No promotional materials for Prolia had been provided by the complainant. The Panel therefore ruled no breach of the Code.

The Panel noted that the complainant might have been referring to the inverted black triangle symbol which when required by the licensing authority on promotional material denoted that special reporting was required in relation to adverse events. The Panel noted Amgen's submission that whilst Prolia was subject to special reporting all promotional material displayed the inverted black triangle symbol. The Panel noted that the European Medicines Agency (EMA) removed the black triangle reporting requirements for Prolia on 25 April 2013 and therefore this requirement no longer applied. In any event the requirements in the Code did not apply to patient materials. The Panel noted its comment above about the burden of proof. No promotional materials had been provided. No breach of the Code was ruled which was upheld on appeal by the complainant.

The Panel then considered the allegations about information on side effects in relation to the package leaflet provided by the complainant and the letter from Amgen to the complainant. The Panel noted the complainant's comments about worldwide differences regarding adverse events. The Panel noted that all companies, including Amgen, had to comply with the local regulatory requirements which differed globally. The Panel noted Amgen's submission that the EU determined whether an adverse event should be listed in an SPC based, *inter alia*, on the likelihood of a causal relationship. That an adverse event was listed in the SPC or its equivalent in one country did not automatically mean that it should be listed in those of other countries. The contents of SPCs were a matter for the regulators. The Panel noted that the patient leaflet dated March 2012 listed as a rare side effect 'persistent pain and/or non-healing sores of the mouth or jaw'. The SPC listed osteonecrosis of the jaw as a rare adverse event. Details were also given in Section 4.4 Special warnings and precautions for use.

The Panel noted the correspondence sent by Amgen to the complainant and did not consider that it was misleading or otherwise an unfair reflection of the SPC with regard to adverse events and the complainant's experience with mouth ulceration and suspected lichen planus. The Panel ruled no breaches of the Code. Two of those rulings were appealed by the complainant but upheld by the Appeal Board. The complainant also alleged a breach that when promotional material referred to published materials, clear references must be given. The Panel noted that no promotional material for Prolia has been provided by the complainant. No breach of the Code was ruled, which was upheld on appeal by the complainant.

The Panel noted its comments and rulings above. It was most unfortunate that the complainant was concerned about Amgen's conduct. However, the Panel did not consider that Amgen had failed to maintain a high standard of conduct. The company had written to the complainant and to her physician to explain the position. The Panel ruled no breach of the Code and subsequently no breach of Clause 2, which were upheld on appeal by the complainant.

In the complaint against Amgen and GlaxoSmithKline the Panel examined the leaflet provided by the complainant. According to Amgen, the patient leaflet provided by the complainant was part of its support programme for patients who had been prescribed Prolia.

The Panel noted that the booklet 'Understanding Osteoporosis' had been sponsored by both Amgen and GlaxoSmithKline as part of its Prolong Patient Support programme. The booklet discussed the Prolong programme, managing osteoporosis; exercising and continued to maintain strong bones and possible side-effects. The section on side-effects listed 'Common side effects', 'Uncommon side effects' and 'Rare side effects'. Rare side-effects (affected 1 to 10 users in 10,000) included persistent pain and/or non-healing sores of the mouth or jaw. The list of side effects was followed by 'If any side effects get serious or if you notice any side effects not listed here, tell your doctor or pharmacist' and 'See Package Insert Leaflet for further information'.

The Panel noted Amgen's submission that the reference in this booklet to persistent pain and/or non-healing sores of the mouth or jaw was intended to describe the rare adverse event of osteonecrosis of the jaw in patient friendly language. In this regard, the Panel considered that the patient booklet was a fair reflection of the UK SPC and ruled no breach of the Code.

The Panel noted its ruling above and considered that neither Amgen nor GlaxoSmithKline had failed to maintain high standards nor that a ruling of a breach of Clause 2 was warranted. No breaches of the Code including Clause 2 were ruled.

A patient who had been prescribed Prolia (denusumab) complained about the information which Amgen UK Limited had supplied about the medicine. Prolia was indicated, *inter alia*, for the treatment of osteoporosis in postmenopausal women at increased risk of fractures. The matter was subsequently taken up with GlaxoSmithKline UK Limited which co-promoted Prolia.

COMPLAINT

The complainant explained that in August 2012, she was injected with Prolia at a local hospital but before agreeing to treatment she made thorough enquiries at the metabolic bone clinic and was told that the only side effects were listed in the leaflet issued by the national patient support group, which were inaccurate and incorrect (a copy of the leaflet was provided).

The complainant stated that she was also given a leaflet which was not written in English, so she could not identify any further side effects not listed in the leaflet from a national patient support group. The consultant wrote a note to this effect on a form which she completed to Amgen and did not receive any acknowledgement when she complained of this fact. she also raised this issue with her consultant at the clinic and gave him the leaflet she had been handed after the injection. The complainant read the leaflet and agreed that it was not printed in English. The complainant's consultant stated he/she would address this with Amgen.

The complainant stated that within three to six weeks, she began suffering side effects that were not listed on the osteoporosis information supplied by Amgen after commencing treatment; by that time she had cracks at the side of her mouth, severe ulceration in her mouth and tongue for no apparent reason other than the use of Prolia, but was unable to find any relief from the medical profession. In desperation the complainant rang the patients help line at the national patient support group and was informed that this was a side effect of Prolia together with other side effects not listed on information given to patients before treatment. The complainant stated that she was also told that there was a yellow card marker on Prolia. The complainant submitted that at no time was she told that Prolia was still under trials; was not given an opportunity to make an informed decision and was therefore not aware of the hazard likely to occur after the administration of Prolia.

The complainant stated that she asked her consultant to write to Amgen to ascertain what the symptoms of other patients were (who had also reported the same side effects as her). The complainant did not have a copy of her consultant's letter to Amgen but she did have a copy of Amgen's not very satisfactory, reply: her consultant agreed that the complainant could contact Amgen which she did in August 2013.

In October 2013 the complainant received an acknowledgement from Amgen (copy provided). In its reply to her consultant, Amgen appeared to deny all knowledge of this ulceration and only referred to ONCJ (osteonecrosis of the jaw) which was mentioned in the osteoporosis leaflet. The booklet provided by Amgen after Prolia had been administered, clearly listed non-healing sores in the mouth as a 'rare side effect'. These statements were ambiguous and Amgen would appear to be trying to conceal the truth (the complainant provided a copy of her letter to Amgen).

The complainant had received another letter from Amgen (dated 14/10/13, copy provided) which claimed exemptions under the Code. In the complainant's view this showed further casual dismissal of patients' complaints, when Amgen urged patients to contact it direct should the need arise. This fell far short of any reassurance Amgen gave in promising to assist in answering complaints.

The complainant alleged that Amgen treated patients who attempted to contact it with disdain and the company obviously needed to try and conceal its mistakes by adopting such a contemptuous attitude. Amgen treated patients like 'laboratory rats' by not being honest about the side effects before treatment and the fact that Prolia was still subject to a 'yellow marker'.

The complainant noted that Amgen had advised her to speak to her consultant which she had done, and he/she was unable to help. This was why, with her consultant's approval, the complainant had contacted Amgen for an explanation.

The complainant considered that she had been co-opted onto a trial of which she was unaware. If she had known that there was a 'yellow marker' on Prolia, she would not have agreed to treatment. The complainant submitted that she was unable to make an informed decision without this information.

The complainant submitted that the administration of Prolia had had dire consequences upon her daily life and her quality of life. It was a long hard battle to try and obtain treatment to assist in the relief of the very painful symptoms as the result of Prolia being used. The complainant was still receiving treatment from a local dental hospital in an attempt to alleviate her suffering and had undergone a biopsy on her tongue to ascertain that it was not carcinogenic.

The complainant submitted that all she had been told was that Prolia had affected the auto immune system. Amgen did not make clear the dire consequences this medicine had upon the quality of patients' lives. It even denied there was a problem (other than

osteonecrosis of the jaw (ONCJ). The side effects were listed but patients were only given that information after the treatment had been administered, although Amgen denied their existence in its letter to her consultant.

The complainant stated that surely patients treated with a 'yellow marker' medicine should be told that it was still under trial. Amgen appeared to be trying to deceive patients and co-opt them to submit to treatment without all the correct information to participate in a medicines trial.

The complainant stated that without all the correct, relevant information patients could not make an informed decision as to the possible long term effects the medicines might have on their health and indeed their everyday quality of life. The complainant's attempts to gather the correct information on Prolia had met with obfuscation, denials and refusal to address the issue raised. This situation was completely unacceptable and Amgen should be held to account for the poor dissemination of information on its product and its effects on unsuspecting patients.

The complainant referred to Clause 7.9 of the Code.

When writing to Amgen, the Authority asked it to consider the requirements of Clauses 2, 4.10, 4.11, 9.1 and 22.2 of the Code in addition to Clause 7.9 as cited by the complainant.

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RESPONSE

Amgen expressed its sympathies to the complainant for the unpleasant symptoms she described in the weeks following her Prolia injection, and its disappointment that its actions to date concerning her case had fallen short of her expectations and resulted in a formal complaint.

Amgen stated that it strongly considered that it had not failed to maintain the justifiably high standards expected by the regulatory authorities, the Association of the British Pharmaceutical Industry (ABPI), health professionals, patients and indeed the company itself. Amgen took all matters affecting patient safety extremely seriously and was keen to swiftly conclude this case to the satisfaction of all concerned.

In particular with reference to the complainant's serious assertion that the company had in some way denied knowledge of adverse effects related to Prolia or had attempted to 'conceal mistakes', Amgen categorically stated that this was not the case. Amgen had a rigorous approach to the collection and assimilation of adverse event data in accordance with EU regulations and updated the summary of product characteristics (SPC) and package leaflet when required based on the emergence of new safety risks.

Amgen stated that it had thoroughly reviewed its current and historical clinical development programme for Prolia and had not found any Amgen-supported Prolia trials carried out at the hospital where the complainant was treated. Thus, to Amgen's knowledge, the complainant had never been enrolled in an Amgen-supported Prolia trial. The complainant's consultant, the prescribing physician, confirmed in October that the administration of Prolia to the complainant was not part of any kind of trial.

Amgen stated that it had not been involved in the supply, creation or authorship of any patient materials used by the national patient support group. The only materials it had supplied to the society had been a press release before the launch of Prolia in the UK (May 2010) and the summary report of 'breaking point', an overview of the state of osteoporosis in the UK (May 2011).

Regarding the foreign leaflet given to the complainant Amgen stated that the hospital had confirmed that the Prolia box which contained the dose given to the complainant contained two patient information leaflets, one in English and in German (all Prolia boxes contained two leaflets of which one was in English). The nurse who administered the dose read the English leaflet before giving the injection, and handed the other unopened leaflet to the complainant, not knowing that this second leaflet was not in English. Unfortunately the complainant thus only saw the German version of the patient leaflet. Amgen noted that the hospital had submitted that it had apologised to the complainant on several occasions regarding this incident.

Amgen explained that Prolia was included in the UK 'Black Triangle' product list and had therefore been subject to intense monitoring since it was launched in June 2010.

With the introduction of the new EU-wide additional monitoring scheme, the European Medicines Agency (EMA) determined that Prolia did not meet the criteria for a black triangle product. Consequently, the EMA removed the black triangle reporting requirements for Prolia on the 25 April 2013 when it released the first EU-wide list of medicines subject to additional monitoring.

In accordance with the requirements of Clause 4.10, all Prolia promotional materials included the required statement regarding how adverse events should be reported.

Amgen stated that whilst Prolia was subject to special reporting, as required by Clause 4.11 of the ABPI Code, all promotional material displayed the inverted black triangle symbol.

Amgen stated that when patients participated in trials of its products, information was provided to the investigators on all aspects of the medicine being researched and full informed consent was always obtained from patients prior to their inclusion. However, as stated above, the complainant's treatment was not part of a clinical trial.

Amgen stated that it had not established a causal relationship between Prolia and mouth ulceration

and consequently mouth ulceration was not an identified risk with the medicine.

Amgen constantly monitored all reported adverse events, which were analysed and assessed for any new potential safety risks. When such safety risks were identified, the competent authorities were informed (ie MHRA, EMA etc) and following those discussions, the SPC and other related materials were amended appropriately based on this evidence. This process formed a critical part of Amgen's commitment to comply with Clause 7.9.

Amgen recognised that 'persistent pain and/or non-healing sores of the mouth or jaw' was listed as a rare side effect of Prolia in the patient information leaflet. That description was intended to describe the rare adverse effect of osteonecrosis of the jaw (listed in the SPC) in patient friendly language appropriate for a patient leaflet. Osteonecrosis of the jaw was a rare but recognised adverse effect of anti-resorptive medicines (including Prolia), which could manifest as deep, non-healing mouth sores leading eventually to exposed mandibular or maxillary bone.

Amgen was pleased that the complainant had received expert dental assessment following the persistence of her symptoms. The company could not comment on the complainant's clinical care since her symptoms emerged but it appeared that appropriate steps had been taken to rule out osteonecrosis of the jaw.

Mouth ulceration (or lichen planus), as experienced by the complainant had not, to date, been identified as adverse events with a direct causal association to Prolia and therefore did not appear as established or 'expected' adverse effects in the SPC.

Amgen knew that the Canadian product monograph for Prolia specifically mentioned tongue ulceration and lichen planus as having occurred in less than 1% of patients in the large-scale, phase 3 Prolia trial. Canadian authorities required all adverse events from the trial to be recorded in this monograph regardless of whether they were recognised Prolia-related adverse effects or events that had arisen unexpectedly at some point following Prolia administration. Current EU legislation did not require all adverse events to be listed at such length. Rather, the SPC presented the recognized adverse effects of a medicine identified via thorough assessment of safety data.

In summary, the analysis of safety reports to date had not established mouth ulceration or lichen planus as a recognised adverse effect related to Prolia use. The Prolia SPC had thus not been updated with regard to mouth ulceration and there were no current plans for a future update to include this as a specific side effect. However, should such safety risks appear in future Amgen would take all appropriate steps to amend Prolia materials accordingly to ensure paramount commitment to patient safety was maintained.

Amgen stated that as a pharmaceutical company which operated in accordance with the Code, its direct involvement with patients was limited. A patient support programme was one way by which additional education and support could be provided to patients and in that regard the company provided a patient support programme, PROLONG, to patients via their treating clinician. This programme provided further information on their postmenopausal osteoporosis, related conditions and lifestyle changes, as well background information on Prolia. The PROLONG programme operated in accordance with ABPI guidance outlined in 'Guidance notes for patient safety and pharmacovigilance in patient support programmes'. The programme was entirely voluntary and to ensure patients were not influenced inappropriately on what treatment they should receive, they could not enrol unless they had already been prescribed Prolia. Once enrolled, patients then directly received the information that the programme offered. Given that the copies of patient material provided by the complainant displayed the PROLONG logo across the top border, Amgen assumed that she was enrolled on this programme by her clinician. Amgen submitted that the PROLONG patient support programme provided a valuable resource to any patient prescribed Prolia and demonstrated the company's commitment to patients by providing education and support to help ensure they got the most out of its medicines.

Amgen stated that it considered that it had upheld its requirements in adverse event reporting, risk management follow up and appropriate responses to health professionals and the public in accordance with the Code. For example, regarding medical information responses, in this case the following process was followed: Amgen replied to enquiries about Prolia in accordance with the Code (Clause 22.3) and The Pharmaceutical Information and Pharmacovigilance Association (PIPA) guidelines. Medical information received a request for information directly from the complainant on 27 August 2013. In accordance with the Code (Clause 22.3), Amgen informed the complainant that she should discuss any personal medical matters with her treating physician. Simultaneously, Amgen contacted the treating physician to tell him about the complainant's concerns so that the matter could be appropriately discussed between the two.

Amgen considered that it had complied with the Code, both in general and specifically in relation to the clauses cited by the Authority, including Clause 2. Amgen again offered its sympathies to the complainant for the symptoms she had endured and for her dissatisfaction with Prolia and Amgen to date. Amgen hoped the above information reassured the complainant of the appropriateness of the company's conduct and how seriously and carefully it considered all matters of patient safety. Amgen would continue to rigorously monitor all adverse event data generated by the use of its medicines and take appropriate action should new risks be identified.

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On receipt of Amgen's response it was noted that Prolia was co-promoted with GlaxoSmithKline UK Limited. Some of the enclosures provided by Amgen included the names of both companies

and so the matter was additionally taken up with GlaxoSmithKline. When writing to GlaxoSmithKline the Authority asked it to consider the requirements of Clauses 2, 4.10, 4.11, 9.1 and 22.2 of the Code in addition to Clause 7.9 as cited by the complainant.

RESPONSE

GlaxoSmithKline explained that Amgen Europe was the marketing authorization holder for Prolia and GlaxoSmithKline co-promoted. GlaxoSmithKline stated that it agreed with Amgen's response above and explained that its only involvement in this matter was limited to one of the documents referred to by the complainant which featured both companies' logos. This was an item intended for patients as part of the PROLONG patient support programme, and was received by the patient after the treating clinician has prescribed Prolia and enrolled her in the scheme. GlaxoSmithKline noted that the information on side effects highlighted in this item was consistent with the patient information leaflet at that time.

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Shortly after writing to both companies, the Authority received further information from the complainant.

FURTHER INFORMATION FROM THE COMPLAINANT

The complainant stated that her consultant had forwarded her the reply from Amgen dated 14 October 2013. The complainant stated that she found the contents of the letter alarming and extremely distressing.

The complainant stated that the letter was in direct contravention to the reply sent previously by Amgen where it stated that ONCJ was the only mouth problem created from use on patients of Prolia, which was proved to be an errant deception. Reading the reply, the complainant alleged that Amgen appeared to be withholding the details of the mouth ulceration side effect in the UK in order to obtain a licence to issue the medicine. The company had failed to inform patients that Prolia was still under trial. Surely this company had a duty of care to patients, no matter in which country they resided?

The complainant stated that Amgen gave reasons in its opinion which allowed it to use Prolia without revealing side effects. The company's interpretation appeared to be that it was not legally required to list all side effects under UK regulations, so it had chosen to withhold this information, despite the fact that numerous cases had been reported in other countries. This was an errant disregard of its responsibilities of a duty of care. The complainant stated that this was clearly covered in Clauses 7.2, 7.6 and 7.9. As it was, patients were informed of possible side effects after receiving Prolia.

Further, with reference to Amgen's letter, the complainant reiterated that the leaflet she was given was not written in English which implied that a medicine not licensed for use in the UK was administered illegally to her. Obviously the particular batch administered to her was destined for only the countries in which the side effects were explained. The complainant queried whether Prolia was legally administered to her. This further supported her comments that British patients were being used as part of an experiment. All patients should be informed that the medicine was under trial where ever they resided.

The complainant stated that there were obviously complex conflicts of interests which avoided the issues being raised. The complainant alleged that certain relevant and important information was being withheld which showed a lack of concern and patient care. In the complainant's view, Amgen appeared to be ignoring its 'duty of care' to all patients.

The complainant submitted that she had endured 15 months of agony and discomfort; as she could not eat properly she sometimes had to drink warm drinks through a straw. The complainant stated that she had to follow a very bland diet and had also endured a lot of distress with pain, discomfort and loss of sleep.

The complainant stated that as Amgen had withheld full information on Prolia's possible side effects, none of the medical practitioners consulted knew that her symptoms were related to the administration of Prolia. As a result, the complainant had had to consult numerous professionals in an attempt to diagnose the problem. A professor at the local dental hospital helped to relieve the symptoms, as did her own GP. The complainant stated that she needed to know how long this discomfort would continue. Could Amgen offer a cure as it was responsible?!

The complainant considered that the national patient support group needed to be commended for giving her this very important information, no one else was either able or willing to admit that ulceration was a side effect.

The complainant found that the most upsetting and distressing aspect was that, in full knowledge that the fact she had reported were true, Amgen denied that it existed. It was also compounded by the fact that Amgen chose not to inform any UK patient.

The complainant objected to being deceived by Amgen, which appeared to do an excellent job of treating UK citizens as second class. This of course did very little for customer relations.

The complainant was unable to respond to Amgen's letter to her consultant as Amgen had made it quite clear that it was not prepared to discuss any concerns or issues with the patient being used in its trials.

Urgent amendments were required to inform all patients of the serious consequences which could arise from the use of Prolia, also that Prolia was still under trial before they submitted to treatment.

Amgen was failing patients and failing to adhere to its legal obligations in the care of patients. What Amgen had done was evil and cruel in marketing Prolia knowing that it could cause the terrible suffering. The complainant stated that it was still causing severe and debilitating side effects which impacted upon the quality of her and her family's life, and which would continue for some considerable time. Being used in this manner by Amgen had had severe effects upon her mental and physical well being.

The complainant was extremely concerned that Amgen considered that it was allowed to market Prolia in the UK without giving full information on possible side effects. Even worse, patients were not informed that Prolia was still under trial. The complainant understood that this information was available to patients in other countries and requested a full investigation into the conditions relating to the release of Prolia in the UK.

The complainant noted Amgen's statement that mouth ulceration had been reported as a rare side effect of Prolia. However, as patients and clinicians were not informed of this possible side effect, it might have occurred without being connected to the use of the medicine particularly as it might be used on people less able to associate their condition with the use of the medicine due to age, ill health or infirmity. In the complainant's case, it had taken visits to a number of medical professionals as well as invasive tests to establish the likely cause of her symptoms. All of this would not have been necessary had she been informed of the possibility beforehand, or at least been given some guidance after the event, rather than receiving flat denials from Amgen.

Amgen had created an international demarcation line of what it considered relevant to the majority of regulations covering the care of UK patients and a lack of consideration for patients' welfare. No-one, whatever their nationality, colour or creed should be treated in this manner - pain and discomfort were universal, no-one was impervious to it.

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FURTHER RESPONSE FROM AMGEN

Amgen noted the complainant's allegation that its letter to the complainant's consultant was inconsistent with the reply given by the nurse that treated the complainant.

- Amgen's letter to the complainant's nurse, 11 June 2013, was in response to specific questions about the frequency of mouth ulcers and details of the company's experience of such symptoms in association with Prolia. Amgen researched the EU and US prescribing information for Prolia and informed the nurse that there was limited information regarding mouth ulceration following use of Prolia. In circumstances where the national patient support group had notified the nurse that treated the complainant of some reports of mouth ulceration from Canada, Amgen tried unsuccessfully to research this issue.
- Amgen's letter (14 October 2013) was in response to a request from the complainant's consultant, about the difference between the Canadian and UK prescribing information for Prolia, and explained that the product information for a medicine might be slightly different in different territories as a result of compliance with the requirements of the various regulatory authorities.

Amgen submitted that there was no contradiction and both letters stated that mouth ulceration was not an expected side effect as per the UK SPC. The two letters were sent from and directed to different individuals and covered different issues: the letter to the nurse who treated the complainant identified the research done by Amgen and stated that it had been unable to research the Canadian reports mentioned by the national patient support group; and the letter to the complainant's consultant dealt with differences between the UK and Canadian prescribing information for Prolia.

The content of an SPC and a patient information leaflet was determined by local and regional regulatory requirements and assessments undertaken by the relevant regulatory authorities. It was therefore inevitable that the product information approved by a regulatory authority and put into circulation in one territory would not be the same in all respects as that approved by a different regulatory authority in another territory. Amgen noted that the product information in the Prolia SPC and patient information leaflet used in the UK, per the centralised procedure, was the same as that used throughout the EU.

Amgen submitted that the position with respect to the inclusion of information about potential adverse reactions associated with the use of a medicine was particularly complex. In some countries, such as Canada, all possible adverse reactions (where a health professional had concluded that a causative relationship might be present) were included in the comprehensive product monograph (the equivalent of the SPC in Europe). Consequently, numerous potential adverse events reported from clinical trials were listed, even where it was not known whether the trial participant actually received the product in question or placebo. The EU determined whether an adverse event should be listed in the SPC based on a range of factors including the severity of the reaction, the numbers of reports and the likelihood of a causative relationship with use of the medicine. The provision of long lists of possible adverse reactions, without thorough assessment of their association with the medicine in the context of all the accumulated safety data, might not help prescribers and patients and might detract from other important information.
The product information contained in the SPC and patient information leaflet for Prolia (including the warnings of potential adverse reactions) was fully approved by the competent regulatory authorities as properly reflecting the available scientific data, before being put into circulation.

Amgen took the proper investigation and assessment of potential adverse reactions very seriously. Individual reports of adverse events, like

those of the complainant, received by Amgen were captured on the global safety database and reported to the regulatory authorities as required by law. Additionally, scientists and physicians at Amgen regularly reviewed all reports on the database to determine if there was any evidence to indicate a new safety risk with a product. Individual cases were medically reviewed together with information in the scientific literature and, as explained above, if the evidence suggested a risk the company would liaise with the regulatory authorities to suggest amendment to the product information. In parallel, the EU regulatory authorities, independently of the licence holding company, also monitored safety data and required SPC amendments when they concluded they were justified.

Amgen was, for obvious reasons, unable to advise in relation to the complainant's particular condition or to provide information on the likely duration of her symptoms. Cases of mouth ulcer had been reported only very infrequently in association with use of Prolia and the evidence to date was not sufficient to reach a conclusion about a causative relationship or to require the SPC to be changed. Amgen submitted that there were many causes of mouth ulceration, unrelated to Prolia and in these circumstances it would be inappropriate for Amgen to comment on the likely outcome in the complainant's case.

In summary, while Amgen understood the complainant's frustration, the evidence available to Amgen had not indicated that a warning in relation to mouth ulceration in association with Prolia was appropriate. The company would, of course, review its product information in the context of all reports of adverse events including the symptoms experienced by the complainant.

Amgen noted the complainant's belief that she was unknowingly included in a Prolia clinical trial. Amgen reiterated that, to its knowledge, the complainant had never been enrolled in an Amgen supported Prolia trial.

The complainant also suggested that the Prolia administered to her might not have been licensed for use in the UK, given that the leaflet provided to her was not in English. Amgen had addressed this issue above, based on the information provided to it by the nurse that treated the complainant, although the source of the product administered to the complainant was a matter for the local hospital, rather than for Amgen.

Amgen considered that it had fully answered all of the questions relating to Clauses 2, 4.10, 4.11, 7.9, 9.1 and 22.2. In particular, it considered that it had complied with all requirements with respect to appropriate responses to the consultant, nurse and the complainant in accordance with the Code.

Finally, Amgen again expressed its sympathy to the complainant in relation to the unpleasant symptoms and distress that she had experienced.

Case AUTH/2647/10/13

FURTHER RESPONSE FROM GLAXOSMITHKLINE

GlaxoSmithKline reiterated that Amgen Europe held the marketing authorization for Prolia and that GlaxoSmithKline co-promoted it; GlaxoSmithKline's involvement was limited to certification of the Prolong booklet.

GlaxoSmithKline considered that the complainant's further comments were addressed towards Amgen – as such it considered it had no further involvement in the matter; Amgen agreed with this position.

GlaxoSmithKline expressed its sympathies to the complainant for the symptoms that she had endured

PANEL RULING

The Panel noted that the complainant was a patient who considered that she had experienced an adverse event as a result of the administration of Prolia. The Panel noted that invariably such individuals were only moved to complain when they felt strongly about a matter. The Panel noted that whilst the complainant raised a number of matters it could only consider those which fell within the scope of the Code. Patient safety was extremely important. It was not clear whether the patient had reported the side effect under the yellow card scheme but she had discussed the matter with various health professionals and been in contact with Amgen. The relevant procedures at Amgen should have ensured that the data was dealt with appropriately.

The Panel noted the relationship between Amgen and GlaxoSmithKline in relation to the promotion of Prolia. It further noted GlaxoSmithKline's submission that its role was limited to the Prolong booklet and the Panel considered that aspect of the complaint in relation to both companies.

Case AUTH/2645/10/13

The complainant's general concern was about the alleged failure to provide information about side effects prior to the administration of Prolia and the failure to provide appropriate information in subsequent correspondence.

The Panel noted that the complainant's physician was responsible for her clinical care and associated matters. Pharmaceutical companies were only responsible under the Code for matters which came within its scope including the provision of material for patients. Clause 22 of the Code covered relations with the public and the patients. Clause 22.3 stated 'Requests from individual members of the public for advice on personal medical matters must be refused and the enquirer recommended to consult his or her own doctor or other prescriber or other health professional'.

The supplementary information referred to not intervening in the patient/doctor relationship and

referred to the need to take particular care with regard to enquiries about side-effects. Amgen had provided information to the complainant and to the complainant's physician.

The Panel noted Amgen's submission that it had not been involved in any patient materials used by the national patient support group.

The Panel noted the complainant's concern that she had been provided with a patient leaflet after the medicine had been administered. The package leaflet supplied was in a foreign language and the complainant had provided a copy. Clause 1.2 stated that the term 'promotion' did not include the labelling on medicines and accompanying package leaflets insofar as they were not promotional for the medicines concerned; the contents of labels and package leaflets were covered by regulations. Clause 1.2 also excluded SPCs from the definition of promotion.

The Panel noted Amgen's explanation; the Prolia box had two patient leaflets, one in German and one in English. The health professional who administered the product read the English version, handing the unopened German version to the complainant. According to Amgen the hospital had apologised to the complainant about this matter. The medicine package contained an English language version of the package leaflet which should have been provided to the complainant. That the health professional failed to do so was not Amgen's responsibility under the Code. The Panel considered that this matter was most unfortunate and had caused the complainant distress. Nonetheless, the Panel considered that both the content of non-promotional package leaflets and the provision of the wrong version to the complainant were not matters that Amgen was responsible for under the Code. The Panel ruled no breach of Clauses 22.2 and 9.1 as both matters were outside the scope of the Code.

The complainant appeared to be under the misapprehension that she was on a clinical trial sponsored by Amgen. That was not so. Amgen submitted that it had not found any Amgen supported trials at the hospital and the complainant's physician had confirmed that the administration of Prolia was not part of any trial. The product had a marketing authorization. It appeared from the complaint that this misunderstanding might have arisen when the complainant was advised by a patient organisation that there was a 'yellow card marker on Prolia'. The complainant alleged that Amgen was not being honest about the fact that Prolia was subject to a yellow marker. The Panel assumed that the complainant was talking about the yellow card scheme by which suspected adverse events could be reported to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Panel noted that the yellow card scheme applied to, *inter alia*, all medicines and vaccines irrespective of how long they had been on the market. Clause 4.10 required all promotional material to include a prominent statement about reporting adverse events under the yellow card scheme. This requirement currently only applied to promotional materials.

The Panel noted Amgen's submission that all Prolia promotional materials included the required statement regarding how adverse events should be reported. The Panel noted that the complainant bore the burden of proving her complaint on the balance of probabilities. No promotional materials for Prolia had been provided by the complainant. The Panel therefore ruled no breach of Clause 4.10 in this regard.

During its consideration of this aspect the Panel noted that changes to the Code which were to come into effect on 1 May 2014 would require patient materials to include details of how to report side effects (Clause 23.3, 2014 Code).

The Panel noted that the complainant might have been referring to the inverted black triangle and Clause 4.11 which stated that when required by the licensing authority all promotional material must show an inverted black triangle to denote that special reporting was required in relation to adverse events. The Panel noted Amgen's submission that whilst Prolia was subject to special reporting all promotional material displayed the inverted black triangle symbol as required by Clause 4.11. The Panel noted that the European Medicines Agency (EMA) removed the black triangle reporting requirements for Prolia on 25 April 2013 and therefore this requirement no longer applied. In any event the requirements in Clause 4.11 did not apply to patient materials. The Panel noted its comment above about the burden of proof. No promotional materials had been provided. No breach of Clause 4.11 was ruled.

The Panel then considered the allegations about information on side effects in relation to the package leaflet provided by the complainant and the letter from Amgen to the complainant. The Panel noted the complainant's comments about worldwide differences regarding adverse events. The Panel noted that all companies, including Amgen, had to comply with the local regulatory requirements which differed globally. The Panel noted Amgen's submission that the EU determined whether an adverse event should be listed in an SPC based, *inter alia*, on the likelihood of a causal relationship with use of the medicine. That an adverse event was listed in the SPC or its equivalent in one country did not automatically mean that it should be listed in those of other countries. The contents of SPCs were a matter for the regulators. Clause 3 included a requirement that promotion was not inconsistent with the SPC and Clause 22.2 included a requirement that information for the public was factual and presented in a balanced way. The supplementary information listed the requirements of Clause 7 which also applied to information to the public. The Panel noted that the patient leaflet dated March 2012 listed as a rare side effect 'persistent pain and/or non-healing sores of the mouth or jaw'. The SPC listed osteonecrosis of the jaw as a rare adverse event. Details were also given in Section 4.4 Special warnings and precautions for use.

The Panel noted the correspondence sent by Amgen to the complainant and did not consider that it

was misleading or otherwise an unfair reflection of the SPC with regard to adverse events and the complainant's experience with mouth ulceration and suspected lichen planus. The Panel ruled no breach of Clauses 7.2, 7.9 and 22.2 on this point. The complainant also alleged a breach of Clause 7.6 which stated that when promotional material referred to published materials, clear references must be given. The Panel noted that no promotional material for Prolia had been provided by the complainant. No breach of Clause 7.6 was ruled.

The Panel noted its comments and rulings above. It was most unfortunate that the complainant was concerned about Amgen's conduct. However, the Panel did not consider that Amgen had failed to maintain a high standard of conduct. The company had written to the complainant and to her physician to explain the position. The Panel ruled no breach of Clause 9.1 and subsequently no breach of Clause 2.

Cases AUTH/2645/10/13 and AUTH/2647/10/13

The Panel examined the leaflet provided by the complainant. According to Amgen, the patient leaflet provided by the complainant was part of its support programme for patients who had been prescribed Prolia.

The Panel noted that the booklet 'Understanding Osteoporosis' (ref DMB-GBR-AMG-037-2012/UK/DNB 0002g/12/32043984) had been sponsored by both Amgen and GlaxoSmithKline as part of its Prolong Patient Support programme. The booklet discussed the Prolong programme, managing osteoporosis; exercising and continued to maintain strong bones and possible side-effects. The section on side-effects (page 18) listed 'Common side effects', 'Uncommon side effects' and 'Rare side effects'. Rare side-effects (affected 1 to 10 users in 10,000) included persistent pain and/or non-healing sores of the mouth or jaw. The list of side effects was followed by 'If any side effects get serious or if you notice any side effects not listed here, tell your doctor or pharmacist' and 'See Package Insert Leaflet for further information'.

The Panel noted Amgen's submission that the reference in this booklet to persistent pain and/or non-healing sores of the mouth or jaw was intended to describe the rare adverse event of osteonecrosis of the jaw in patient friendly language. In this regard, the Panel considered that the patient booklet was a fair reflection of the UK SPC and ruled no breach of Clause 22.2 of the Code.

The Panel noted its ruling above and considered that neither Amgen nor GlaxoSmithKline had failed to maintain high standards nor that a ruling of a breach of Clause 2 was warranted. No breach of Clauses 9.1 and 2 was ruled.

APPEAL FROM THE COMPLAINANT

The complainant stated that she suffered an adverse reaction immediately after receiving the injection in August 2012. Her blood pressure was elevated and she was admitted for observations.

The complainant stated that she was hospitalised as a result of an adverse reaction to Prolia and that Clause 7.9 had been breached. As this occurred in 2012 the 'black triangle' system was in force and was clearly displayed in the companies' documents and leaflets. The complainant alleged a further breach of Clause 7.9 in that Amgen did not make the full information available to prospective patients, only company promotional material. As a result patients could not make informed, constructive decisions as to their treatment. The recorded adverse effects must reflect the available evidence as stated in Clause 7.9.

The complainant stated that she had informed her consultant of her adverse reactions to Prolia in September 2012, additionally he/she was not even aware that she had been admitted to hospital after the injection! The complainant alleged that her consultant did not inform Amgen until one year after the event, despite the complainant asking him/her to do so at the time of the consultation. The complainant alleged that this again was in breach of regulations which stated that all adverse effects should be reported. This information in the case of UK residents appeared to be suppressed.

The complainant stated that Amgen had replied to her query one year after the regulations had changed. The complainant stated that her enquiry was initiated in 2012, when the black triangle marker was still in evidence.

The complainant alleged that Amgen still continued to dismiss a valid complaint which was initiated in 2012 and as such she alleged a breach of Clause 4.11, in that additional monitoring was required in relation to adverse reactions.

The complainant alleged that her complaint was reported within the timescale (2012) to the consultant in charge of her treatment at the time as per the company directives. The black marker regulations were clearly evident and required patients/consultants to submit adverse reactions.

The complainant stated that she did not receive a reply in 2012, and in 2013 she again raised this with her consultant; who agreed to contact Amgen, however it appeared that he/she delegated this task to the nurse that had treated her.

The complainant alleged that she was not informed at any time that there was a 'yellow marker' in force in 2012. This matter had not been addressed or explained by Amgen and was clearly in breach of the regulations.

The complainant alleged that she was not properly informed of adverse reactions until after receiving treatment. This information was apparently available to patients in other countries.

The complainant alleged that UK citizens were not being treated fairly, in breach of Clause 7.2. The evidence available to the company was not reflected in the material made available to patients, and leaflets were not sufficiently complete to enable patients to be able to form their own opinions.

The complainant alleged that there appeared to be no help or co-ordination to assist local medical practitioners, who were left with the problems of administering a new medicine and its consequent possible adverse reactions. Amgen appeared to have withheld information as to a medicine's adverse reactions and left its problems for the NHS to solve. Consultants appeared to have withheld information as to a medicine's adverse reactions from Amgen to the detriment of patients.

The complainant stated that the national patient support group was an accredited organisation. The complainant alleged that Amgen had compounded serious deceptions by the organisation and those who supported it. If the company was aware of these apparent errors, as stated, why did it not give the national patient support group the correct information? The complainant queried whether consultants who regularly lectured at the national patient support group meetings were giving the 'incorrect' information.

The complainant alleged that with regard to the statement by the nurse, she did not know that the Prolia pack contained two leaflets. This was brought to the complainant's attention by this complaint. The complainant had only spoken to this nurse on one occasion (in 2013) since the incident, in the presence of her consultant, and a witness who accompanied the complainant to this appointment because of ill-health. However, as a result of this incident the complainant had emailed the nurse (5/1/2014 copy provided) to ask for a copy of the English version, which he/she supplied. Presumably, this was the 2013 version and not the 2012 leaflet.

The complainant agreed that handing out incorrect literature was the responsibility of the hospital. The fact however did not cover what was or indeed what was not contained in the document.

The complainant noted that the legislation regarding the black triangle was still in operation in August 2012, when she received her initial treatment. The complainant had requested information about mouth sores and ulceration in September 2012. This complaint was confirmed to exist in 2013 by Amgen's letter so it was relevant to this case in 2012. The information was denied and this was clearly a breach of Clause 7.9. The complainant stated that she still suffered from severe sores and ulcerations of the mouth and the symptoms were not clearing and questioned if this was a precursor to ONCJ. The complainant considered that this adverse reaction was recognised and should be included in the company's literature. It appeared that further research by the company was required.

The complainant alleged that [Prolia] was subject to special reporting of adverse reactions (no matter how rare), when it was administered in 2012 and she was not informed. The complainant had a letter dated October 2012 from Amgen which confirmed her registration on the program (copy provided) and a further letter from Amgen, dated January 2014 to confirm that she had registered on the program so Amgen knew about her.

The complainant alleged that Amgen should exercise a moral conscience as it appeared to be unaware of this adverse reaction. There had been reports of [mouth] ulceration and non-healing mouth sores in the UK, USA and Canada from patients.

The complainant alleged that it was apparent that in other countries patients were at a loss as to who to turn for help, so it appeared that Amgen had failed international patients in addition to those in the UK (blog articles were provided).

The complainant alleged that the only additional information on Amgen's website was about skin infections which the complainant alleged she had also developed. At her consultant's instigation, the complainant was referred to a dermatologist and her consultant had a copy of this report.

The complainant alleged that the mouth ulceration and non-healing mouth sores appeared to be a common complaint of reported to the UK, USA and Canada. It would therefore be difficult and negligent for Amgen to ignore this as an adverse reaction, particularly as they could be a precursor to ONCJ. Amgen had a moral responsibility to patients to record all information, as Prolia was available worldwide. The complainant alleged a breach of Clause 7.9 as the available clinical evidence had not been disseminated to patients.

The complainant questioned why Amgen had reported the skin infections which were included on its recent updates but not include mouth ulceration and lichen planus as it had admitted that these existed. The complainant alleged a breach of Clause 7.2 as the material was not sufficiently complete for patients' information.

The complainant questioned why, from all the evidence in its possession from the UK, US and Canada that these adverse effects had occurred in patients, was it not included in Amgen's information to patients and prospective patients? Amgen appeared to be duty bound under Clause 7.2 and 7.9 to include this information. It was Amgen's responsibility to ensure the correct information was made available, even though it appeared to operate a 'selective' information pack for UK citizens.

The complainant questioned the statements by Amgen as from the information obtained from other countries, (blog articles were provided) its apparent lack of honesty left a lot to be desired.

The complainant questioned why Amgen appeared to dismiss the data amassed from other countries. Prolia was available worldwide and all patients were entitled to the same consideration whichever country they lived in. Cherry picking the regulations did not help the patients when they were suffering.

The complainant alleged that on all the literature supplied by Amgen, it recommended that all adverse effects should be reported. Although when this was done, Amgen did not appear to be able to offer any remedy to cure the suffering.

The complainant alleged that by admitting that Amgen was prepared to allow the national patient support group to proceed with the incorrect information, it had compounded a deception by not informing it. The national patient support group was the main distributor of all types of literature applicable to the treatment of osteoporosis and by not informing it of the correct information to convey to unsuspecting patients, this fell far short of its purported high standards.

The complainant was still concerned that her questions were not answered by Amgen in 2012 and this had still not been addressed or answered; the complainant queried whether this was because she was a UK resident.

The complainant alleged that when she received the treatment in August 2012, the black triangle system was still in existence for Prolia and therefore was relevant to her treatment and the adverse effects sustained.

The complainant questioned Amgen's statement in respect of the reporting of adverse effects as it would only receive comments from consultants. With the consequent result that this information was much delayed. The complainant considered that the reporting of adverse effects was over complicated and daunting for many people who suffered and the additional stress from this process was no doubt avoided by many people.

The complainant alleged that mouth ulceration and non-healing sores of the mouth had been admitted by Amgen earlier as a recognised adverse reaction; why did it deny it now? The complainant alleged a breach of Clause 7.9.

The complainant alleged that the admission that mouth ulceration and soreness of the mouth in the leaflet was very misleading to patients. Patients experienced these painful side-effects all over the world.

The complainant alleged that Amgen's explanation in the literature was a clear breach of Clause 7.2 and misled patients and should be remedied on its patient leaflets.

The complainant alleged that in relation to the company not accepting the adverse effect of mouth ulceration as a rare side-effect in the UK, why was it an admitted, reported fact in the US and Canada as per Amgen's letter?

Why had UK/EU patients, been let down by the regulations? The complainant alleged that the company was in breach of Clause 7.9.

The complainant agreed that she was enrolled in the program, indeed she received a further letter in January 2014, but the complainant did not find participation helpful as Amgen did not answer questions, participation was a two way process.

The complainant alleged that Amgen had replied to her enquiry in August 2013 about adverse effects initiated in 2012 when the black triangle system was in force, therefore Amgen's claim under the regulations did not apply.

The complainant alleged a breach of Clause 9.1 in that high standards had not been maintained.

The complainant alleged that Amgen had a moral responsibility to patients to record all information in their literature, as the medicine was available worldwide. The lack of clear unambiguous information was in breach of Clause 7.9.

The complainant queried why, if Amgen had included skin infections in its recently updated literature, it did not include mouth ulceration and lichen planus. The company had admitted that it did exist. This appeared to be a breach of Clause 7.2.

The complainant alleged that the admission by Amgen that mouth ulceration, soreness of the mouth and non-healing sores in its literature and the reference to ONCJ misled patients. Patients worldwide experienced these distressing adverse effects and the implication was that they might be a precursor to ONCJ. This particular paragraph in the company literature misled patients in breach of Clause 7.2.

The complainant stated that her experiences with Prolia and Amgen had been unpleasant and distressing. Not only had accurate information about the medicine not been supplied, the complaint alleged she also suffered a number of 'adverse reactions'.

The complainant alleged that both Amgen and GlaxoSmithKline were international pharmaceutical companies which picked and chose what information to release to patients about all of the adverse reactions patients could experience from the use of their products. The companies' biased responses were detrimental to patients' health and care.

The complainant alleged that the law in relation to the protection of UK citizens had clearly been breached from the lack of disclosure, by the companies' admission. In breaching these regulations, the companies openly admitted a selective policy as far as the release of all the information regarding adverse reactions to this medicine. Without UK regulation and codes of practice patients would be unable to voice their justified complaints and concerns regarding Prolia. The complainant submitted that from the documents recorded by other medical bodies (copies of which were provided), it was considered that insufficient evidence had been gathered to even commence its usage on patients, not only those in the UK. Reported adverse reactions included spontaneous fractures, cancer and problems with bone formation.

The complainant was puzzled as to why the thigh bone was now included in the DEXA scan, now she knew, since the information regarding 'spontaneous' fractures of both the thigh and jaw bone on tooth extraction had been published. This was yet another 'adverse reaction' not disclosed to patients. Patients

should be advised to check the internet for other countries' responses and reported adverse reactions.

The complainant stated that in her case, this would have proven invaluable, as Amgen openly admitted to letting the national patient support group continue to report inadequate literature, without informing them of all the relevant details. Withholding of this crucial information had proved detrimental to the complainant's and other patients' welfare.

The complainant alleged that Amgen's attitude was disconcerting and distressing; it still did not give an account of its actions, it appeared to only take what steps it could to avoid the very real complaints made regarding the adverse effect Prolia had on patients' lives, which the complainant found extremely unnerving.

The complainant stated that, having read other unbiased observations from medically qualified practitioners, which were more honest, she was terrified at the thought of what might happen in the future to her immune system as a result of being treated with Prolia.

The complainant now regretted placing her faith in the information handed out to UK citizens, as it could and probably would have far reaching deterioration on some patients involved in its usage.

The complainant stated that finally all UK members unwittingly participating in the use of Prolia would have to rely on the NHS to help them cope with their 'adverse reactions'. It was fortunate that such dedicated help and professionalism was available.

The complainant alleged that Amgen and GlaxoSmithKline would not be in the least concerned in the eventual fate of their participants. They had still not given a suitable explanation as to why they had not complied with the PMCPA regulations governing UK citizens' rights. Their actions had not been honest or unbiased in respect of the adverse reactions of Prolia.

The complainant stated that she still had an extremely sore mouth, ulceration and a severe skin infection and irritation, effects which had only recently been admitted by this company (web article provided).

The complainant stated that she was a UK citizen and entitled to the regulations quoted by the PMCPA as a right of protection, as other NHS bodies appeared, for some unknown reason, to allow Amgen to publish what it considered relevant. Internationally, this was an extremely irresponsible system to operate.

The complainant alleged that Amgen stated that it had 'no intention' of including this crippling, painful symptom (lichen planus) in UK 'adverse effects'. Surely it was within the PMCPA's remit to enforce and ensure that UK citizens had this knowledge before embarking, on a very destructive road to personal health and welfare, whilst also coping with the original deteriorating illness, for which this so called 'cure' was administered. The complainant hoped that the relevant steps would be taken to avoid other patients suffering unnecessarily as she had done and that in future truthful and unbiased information about Prolia would be freely available.

* * * * *

The complainant was asked to clarify her appeal in respect of which rulings of no breach of Clauses 9.1 and 2 she was appealing and to give reasons for appealing Clauses 2 and 7.6.

* * * * *

The complainant alleged that when she had received Prolia in 2012, it was still subject to the 'black triangle' until April 2013. Therefore all adverse effects should have been the subject of special reporting. The adverse effects the complainant started suffering were reported to her consultant in September 2012. The promotional material misled patients. Patients could not directly report adverse effects to the company. This fact was not clearly stated to patients and was ambiguous in breach of Clause 7.2.

The complainant noted that in 2012 Amgen was subject to special reporting of adverse effects in respect of the black triangle system. The complainant accepted that the promotional material of 2012 did display the black triangle and that Clause 4.10 was not breached.

The complainant alleged that in 2012 the information promoted by Amgen was not accurate, balanced or fair to patients, did not reflect the clinical evidence available to the company and was in breach of Clause 7.2. Patients had reported mouth ulcers and non-healing sores to the mouth in this country and worldwide.

The complainant alleged that Clause 7.9 had been breached by the company in 2012 as the information and claims in respect of side effects did not reflect the available evidence. Evidence was available from patients worldwide that the adverse effect of mouth ulceration and non-healing sores of the mouth had been reported (the complainant cited blog articles previously provided).

The complainant alleged that the material available to patients in 2012 was not sufficiently complete to enable patients to form their own opinion of the therapeutic value of the medicine, in breach of Clause 7.2.

The complainant alleged a breach of Clause 9.1 in that the high standards of the company had not been maintained. The material available to patients in 2012 was not of a sufficiently high standard due to the omissions of certain 'rare side effects' in its material despite evidence from patients worldwide. This could be prejudicial to patient safety and the complainant alleged a breach of Clause 2 in that the material promoted by the company in 2012 did not reflect the available clinical evidence.

The complainant alleged that Amgen had admitted that this adverse reaction had been reported by patients receiving Prolia, yet it stated it still did not intend to publish it. This action was in breach of Clauses 7.2, 2 and 9.1. The material promoted by Amgen was not accurate, fair or balanced in breach of Clause 7.2. As a result of this omission the material might have been prejudicial to patient safety, in breach of Clauses 2 and 9.1 as the high standards of the company had not been maintained.

The complainant noted that GlaxoSmithKline had stated it relinquished responsibility for publishing data. This was not clear in 2012 as both company logos were displayed. In view of GlaxoSmithKline's submission that Amgen was solely responsible for this information, the complainant had no alternative but to request that the appeal continued against Amgen.

The complainant alleged that Allergan knowingly passed inadequate information to other bodies, eg the national patient support group. The company had stated that information 'was taken from a general publication'.

The complainant alleged a breach of Clause 9.1 in that the company had failed to maintain high standards. The company had failed to disclose all of the available information to the national patient support group and patients.

The complainant noted that the material available to patients in 2012 referred only to Amgen and not GlaxoSmithKline. It was unclear whether both companies were involved when this complaint was initiated. GlaxoSmithKline had stated that it was Amgen's responsibility, which was now understood. By not releasing all of the relevant information, Amgen had influenced patient decisions. Not being fully aware of the dangerous, life changing, painful adverse reactions of mouth ulceration, and non-healing sores of the mouth. The company had openly admitted that it had prior knowledge of this adverse effect by stating that it occurred in some patients.

The complainant alleged that Prolia acted on the body's autoimmune system and the complainant categorically stated that she did not have mouth ulceration, non-healing sores of the mouth, skin infection or other painful conditions before she received Prolia.

The complainant alleged that Amgen had misled her and other patients by not revealing this particular adverse reaction, in breach of Clause 7.2. This information should have been released to the public to enable patients to form a balanced opinion. The company encouraged the use of the medicine by withholding this information from patients, in breach of Clause 7.2.

The complainant alleged that no information about the adverse reactions was given to the patient receiving this treatment until after the medicine was administered. Therefore the patient was unable to make an informed decision prior to receiving treatment.

The complainant alleged that this was in breach of Clause 7.2.

The complainant alleged that the detailed information provided in the form of statements of complaint from other patients (worldwide) supported her complaint of insufficient information being available to patients and withholding important adverse reactions on the material being made available to patients.

The complainant alleged that the clauses cited above had been breached and the company openly admitted that it would continue to do so in respect of patients in the UK. By failing to declare, upon request, the percentages of patients who experienced these and other adverse reactions, Amgen had perpetuated a deception. Amgen needed to comply with the Code. Was Amgen so large that it thought that it was exempt from the Code? Surely the Code was in place to protect UK citizens when they were being exploited and exposed to life changing and debilitating adverse reactions. If the Appeal Board did not enforce them - where did patients go?

The complainant alleged that Amgen had attempted to exonerate itself because she did not have sight of its leaflet. This would have been irrelevant as Amgen had admitted that this reported 'adverse reaction' was known, but it had chosen not to reveal it anyway to UK patients.

COMMENTS FROM AMGEN

Amgen noted that the complainant alleged that it had breached Clause 4.11 which required that when requested by the regulatory authority, all promotional material must display an inverted black triangle symbol to denote that special reporting/ additional monitoring of adverse reactions was required. Amgen submitted that as previously explained, promotional material for Prolia displayed the black triangle symbol during the period required by the regulatory authority and as such the company had complied with Clause 4.11.

Amgen noted that the complainant accepted that the promotional material of 2012 displayed the black triangle. However, the complainant appeared to suggest that because Prolia was subject to special reporting as indicated by the black triangle and a 'yellow marker' when she reported mouth ulceration, the company's handling of her adverse event report had been inadequate. This was not so. Amgen provided information on the additional monitoring/ special reporting requirements and the Yellow Card Scheme for the benefit of the complainant.

Amgen submitted that whilst not a consideration under Clause 4.11, all adverse events that were reported to it, irrespective of which product was suspected of being linked to the adverse event, whether the report was made by a health professional or patient and whether the product was subject to special reporting or not, were processed in the same way through its case management system and reported as required to the relevant regulatory authorities.

Amgen noted that the complainant had made various allegations concerning its provision of information relating to Prolia. Specifically, that in breach of Clause 7.2 and/or Clause 7.9:

- Amgen had not made available to prospective patients full information about side effects to enable patients to form their own opinions about the medicine and the information provided about side effects was selective and did not reflect the available evidence;

- The information concerning mouth ulceration and soreness of the mouth in the package information leaflet (PIL) for Prolia was misleading.

Pharmaceutical companies were not permitted to promote prescription only medicines to patients and as such the product information which the company made available to prospective patients in the EU was that contained in the product information designed for health professionals the SPC, and the information contained in the PIL. The promotion of medicines to health professionals was, however, permitted provided it complied with the law and the Code. The focus of Clause 7 of the Code was promotional information directed toward health professionals rather than information made available to the general public; nevertheless, Amgen had sought to address the complainant's concerns.

Amgen submitted that the content and format of information in the SPC and PIL for medicines marketed in Europe was prescribed by law and regulatory guidance and the information listed, including the warnings of potential adverse medicine reactions, was reviewed and approved by the regulatory authorities to ensure that it properly reflected the available scientific evidence, before the product was put into circulation. However, as described previously, the approach taken by the regulatory authorities to the content of SPC and the PIL - which reflected the SPC - was not consistent across the globe. Some countries, such as Canada, mandated that all possible adverse reactions reported during clinical trials were included in the product information. This was not the approach taken in the EU where inclusion of an undesirable effect in the SPC and PIL was based on the totality of a range of factors including the likelihood of a causal relationship with the relevant medicine, the severity of the reaction and the numbers of reports received. Accordingly, the fact that a company received one, or even several, reports of a suspected adverse reaction did not necessarily automatically translate into a warning for that adverse reaction in the SPC or PIL.

Amgen submitted that it had robust processes in place, as required by law, for signal detection and assessment ie processes to determine whether safety information it received was suggestive of a new side effect that should be included in product information and also patient leaflets. The company continuously monitored and evaluated the data available to it. If medical judgment and scientific interpretation of the available data suggested a risk, Amgen liaised with the relevant regulatory authorities to agree an amendment to the product information. In addition to the company review, in Europe, a similar process was also carried out by the regulatory authorities. Regulatory authorities reviewed both the individual reports of adverse reactions sent in by health professionals and patients and the comprehensive safety information reports which companies were required to submit on a periodic basis, so called, periodic safety update reports (PSURs) to determine if a change to the product information was required. PSURs were based on all available data and provided a critical analysis of the risk-benefit balance of the medicine taking into account new or emerging information about a medicine. In addition, the regulatory authority might compare the reporting frequency of a suspected adverse reaction with the expected frequency of the same adverse event in the general population. If the regulatory authority, based on its assessment of the available data, considered that product information should be amended, the company was required to implement the required changes as soon as possible.

Amgen submitted that product information and information for patients was continually updated throughout a product's life-cycle as the safety information reported to the company underwent the scrutiny described above. The safety profile of a product tended to emerge over time as larger and more diverse patient populations were exposed to the product following launch into the market. For example, the product information for Prolia was amended last year to add atypical femoral fracture as a side effect because this rare adverse reaction only became apparent two or so years after launch of the product.

Amgen submitted that contrary to the complainant's assertion, it never stated that it had 'no intention' of including lichen planus as an adverse reaction in the UK SPC. As was the case for all potential adverse reactions reported in association with Prolia, this event was subject to the company's signal detection and safety assessment processes as described above. To date, the evidence had not been sufficient to reach a conclusion about a causative relationship between mouth ulceration or oral lichen planus and Prolia to require these events to be listed in the UK SPC and PIL for Prolia. Amgen would continue to review information on Prolia.

Amgen submitted that as explained previously, the description of 'persistent pain and/or non-healing sores of the mouth or jaw' in the PIL was intended to describe in patient friendly language the rare side effect of osteonecrosis of the jaw (ONJ) which was included in the SPC. The presentation and content of the PIL for Prolia was consistent with the current law and guidance relating to PILs and had been reviewed and approved by the regulatory authority. Whilst Amgen did not believe that the description of ONJ in the PIL was inappropriate, it was currently exploring with the regulatory authority whether the existing description could be changed to further aid patient understanding.

Amgen noted that the complainant had stated that she wished to appeal the Panel's ruling of no breach of Clause 7.6, which required that when promotional material referred to published studies,

clear references was given. The complainant had not, however, provided any reasons as to why this clause was being appealed. Amgen confirmed that clear references were provided on all promotional material, including that relating to Prolia, which referred to published studies.

Amgen noted that the complainant alleged that certain aspects of Amgen's conduct were in breach of Clause 9.1. In particular:

- Amgen permitted the national patient support group to publish incorrect information concerning Prolia;

- Amgen had not paid attention to, or acted upon, patient concerns regarding Prolia which had been posted on International internet forums.

Amgen reiterated that it had not had any involvement in the supply, creation or authorship of any Prolia patient materials published by the national patient support group. Amgen was careful to ensure that it maintained high standards when it interacted with patient organisations by adhering to the requirements of the Code relating to pharmaceutical companies' interactions with patient organisations (Clause 23 of the Code that was in force at the time of the complainant's complaint, Clause 24 of the current Code) and in particular, by respecting its independence.

Amgen submitted that the national patient support group material submitted by the complainant stated that it was last revised in June 2011. It formed part of a general therapy review of available osteoporosis treatments, including Prolia. The possible side effects section of the national patient support group leaflet was not inconsistent with the SPC or PIL for Prolia which was in force at the time.

Amgen submitted that it had acted in accordance with the Code's requirements relating to interactions with patient organisations and it believed that it had upheld the high standards required under Clause 9.1.

Amgen submitted that it did not manage, control or in any way influence the internet sites/blogs referenced by the complainant as part of the appeal; the messages contained were posted freely by members of the public. Pharmaceutical companies were not required to monitor internet sites that were not under their management or responsibility for potential reports of adverse reactions. However, if a company became aware of a report of a suspected adverse reaction from any non-company sponsored site it was required to assess the report to determine whether it should be reported.

Amgen confirmed that the information contained in the blog extracts which the complainant provided as part of the appeal had all been submitted to the company's safety database in accordance with its usual process for handling cases from social media. As described above, all information about possible adverse reactions to Prolia, including this type of information, contributed to the signal detection and assessment process.

Amgen submitted that it had met its obligations with respect to the information brought to its attention and accordingly it had not failed to maintain high standards as required by the Code.

Amgen noted that the complainant contended that the alleged failures to comply with Clauses 7.2 and 7.9, in particular, were prejudicial to patient safety and warranted a breach of Clause 2 of the Code.

Amgen hoped the above information demonstrated that it took the proper investigation and assessment of potential adverse medicine reactions very seriously and had appropriate mechanisms in place to do so. The safety related information in the SPC and PIL for Prolia, which had also undergone competent authority review and approval, reflected the evidence currently available. Amgen assured the complainant that the event experienced by her as well as all other reported potential adverse reactions were considered as part of the company's ongoing monitoring of safety information and that Amgen took appropriate steps to include information on possible risks in the SPC and PIL when medically and scientifically indicated and approved by the regulatory authority.

In summary, Amgen submitted that it had complied with the Code and with its obligations under current safety legislation and good pharmacovigilance practices and that the company had addressed the complainant's appeal of the Panel's rulings of no breach of Clauses 2, 4.11, 7.2, 7.6, 7.9 and 9.1.

FINAL COMMENTS FROM THE COMPLAINANT

The complainant alleged that Amgen had not answered questions in relation to how long a patient had been treated with Prolia before the spontaneous fractures occurred. Amgen had also failed to reply in respect of informing patients regarding the deterioration of bone density. Once this treatment had ceased, there was no mention of this fact in any of the material promoted by Amgen. Amgen had not confirmed that the relevant information for the package was made available or that there was warning of potential adverse reactions before treatment. The company confirmed that details of mouth ulceration and non-healing sores were available to patients in Canada. In its previous submissions Amgen clearly stated that it had no plans for future updates. The complainant noted that Amgen stated that in respect of the national patient support group as to not being involved in the production of any literature, yet Amgen still referred patients to the national patient support group.

The complainant alleged that Amgen's response to the appeal was at variance and did not concur with its response to the complaint.

The complainant alleged that Amgen had admitted it tailored the details of adverse reactions where it could, in order that the minimal details were released. This, of course, was couched in favour of the company's medicine.

The complainant noted that the national patient support group advised patients to exercise in a more gentle form, more suitable for the elderly, whose problems it understood as it worked with them daily.

The complainant noted that Amgen admitted that it used Prolia on a 'worldwide' basis, yet claimed to have no knowledge of the complaints she had sent to it.

Amgen admitted it was aware of the serious, life threatening consequences of continuing its use. Yet after the initiation of the complaint Amgen stated that it did not or could not find the complaints in other countries. Where patients suffered the same adverse reactions as the complainant and, in some cases even worse, but Amgen intended to use the information forwarded by the complainant. The complainant alleged that Amgen purported to be so thorough and concerned for patient welfare, it should have been aware of these complaints when initiated a considerable time ago on the various websites available to be read.

The complainant noted that Amgen stated it would continue to monitor it. It gave the complainant no reassurance that Amgen would take any constructive action to help prevent Prolia's painful path through patients worldwide.

APPEAL BOARD RULING

The Appeal Board considered that patient safety was extremely important. The Appeal Board noted that this was an emotive and important personal issue for the complainant; it was an unfortunate case and the Appeal Board expressed its sympathy for the complainant. However, the Appeal Board noted that its responsibility was to consider this case with regard to the requirements of the Code.

The Appeal Board noted that the complainant raised a number of issues which were not covered by the Code.

The Appeal Board noted Amgen's submission that the EU determined whether an adverse event should be listed in an SPC based, *inter alia*, on the likelihood of a causal relationship with use of the medicine following an analysis of all the available safety data. In that regard, the Appeal Board noted Amgen's submission that in Canada the situation was different in that all possible adverse reactions reported by patients taking the medicine in clinical trials were included in the equivalent document to the SPC, regardless of whether the reaction was related to the medicine or not. The Appeal Board recognised that it might be confusing for the complainant to see different adverse reactions reported in SPCs or equivalent for Prolia in different countries. However, the Appeal Board noted that the contents of SPCs and their equivalents in other countries such as Canada were a matter for each country's regulators.

The Appeal Board noted that the supplementary information to Clause 22.2 stated that the requirements of Clause 7 relating to information, also applied to information to the public. The Appeal Board noted that the patient leaflet dated March 2012 listed as a rare side effect 'persistent pain and/or non-healing sores of the mouth or jaw'. The Appeal Board noted from the representatives of Amgen at the appeal that this wording had been agreed with the regulators as a patient friendly description of osteonecrosis of the jaw as listed on the SPC. The Appeal Board considered that it might not be obvious that this description on the PIL did not cover mouth ulcers or sores arising from anything other than osteonecrosis of the jaw and noted that the Amgen representatives at the appeal stated that the company was discussing with the EMA a possible change to this wording to make the position clearer. The Appeal Board noted that, in any event, the content of SPCs and PILs was a matter for the regulators.

The Appeal Board noted that Amgen had written to the complainant and her treating physician and the company's submission that it had added her reported adverse event to its central files in line with regulatory requirements. The Appeal Board did not consider that the correspondence sent by Amgen to the complainant was misleading or otherwise an unfair reflection of the SPC with regard to adverse events and the complainant's experience with mouth ulceration and suspected lichen planus. The Appeal Board upheld the Panel's ruling of no breach of Clauses 7.2 and 7.9. The appeal on this point was unsuccessful.

The Appeal Board noted there were no reasons provided for the appeal regarding Clause 7.6. No promotional material had been provided by the complainant. Consequently the Appeal Board upheld the Panel's ruling of no breach of that clause. The appeal on this point was unsuccessful.

The Appeal Board again noted that it had not been provided with any promotional material, consequently it upheld the Panel's ruling of no breach of Clause 4.11 with regard to the display of the inverted black triangle symbol. The appeal on this point was unsuccessful.

The Appeal Board noted its comments and rulings above. The Appeal Board noted the complainant's concern but considered that Amgen had not failed to maintain high standards and it upheld the Panel's ruling of no breach of Clause 9.1. The Appeal Board consequently upheld the Panel's ruling of no breach of Clause 2. The appeal on both points was unsuccessful.

Complaint received **20 October 2013**

Case completed **19 February 2014**