ANONYMOUS LILLY EMPLOYEE v LILLY and DAIICHI-SANKYO

Efient press release

An anonymous Lilly employee stated that he was increasingly frustrated at his company and had reached his limit with the consumer press release issued by Lilly and Daiichi-Sankyo to mark the launch of Efient (Prasugrel).

Prasugrel was a good medicine but needed to be used with caution. There could be significant issues with bleeding but these could be minimised by carefully considering the patient. Indeed, the marketing authorization required a risk minimisation programme to be carried out. The consumer press release, emphasised the deserved superior efficacy of prasugrel over clopidogrel [Plavix, marketed by Sanofi-Aventis] but made a cheap point about 25% resistance when it was well known that this study was from a 60 patient study in primary percutaneous coronary intervention (PCI). The safety section described bleeding as epistaxis, haematuria when actually there were significant higher fatal and life threatening and minor and major bleeds. In an attempt to dislodge clopidogrel from its pedestal, Lilly appeared ready to sacrifice safety, pushing the use of this medicine beyond its PCI indication.

The Panel noted that the press release briefly described the indications for Efient and the efficacy data which had led to the approval of the medicine by the regulatory authorities. Some background information was given as to the prevalence of acute coronary syndrome (ACS) and the economic impact of heart disease. The press release was not an advertisement per se for Efient and so in that regard the Panel ruled no breach of the Code.

Readers were informed that despite current guidelines, and evidence of efficacy, therapy was underused. The National Institute for Clinical Excellence had recommended that patients with ACS be treated with aspirin and clopidogrel. It was noted, however, that up to 25% of patients did not respond adequately to clopidogrel.

In response to a request for further information, Lilly and Daiichi-Sankyo had submitted that although it was clear that there was a variability of response to clopidogrel, the percentage variability varied widely because there was no agreed threshold of platelet inhibition below which a patient would be considered a non-responder and no one standardized method by which to measure platelet inhibition. The companies had cited what they considered to be a relatively conservative estimate with regard to the percentage of patients who were non-responders ie 25%. O'Donoghue and Wivott (2006) reported that between 4% and 34% of patients had been deemed to respond inadequately to clopidogrel depending on the method of testing and the definition of 'resistance' or 'hyporesponsiveness' used. The Panel noted that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, the Code required special care to be taken to ensure that the issue was treated in a balanced manner. The Panel considered that the statement in the press release 'research has also shown that up to 25% of patients do not respond adequately to clopidogrel' did not adequately reflect the situation and in that regard was misleading; high standards had not been maintained. Breaches of the Code were ruled.

In a section of the press release headed 'Method of action' it was stated that there was a risk of bleeding with all antiplatelet medicines and that prasugrel had an increased risk of bleeding compared with clopidogrel. The common bleeding events were described. It was also stated that treatment should only be prescribed to patients at increased risk of bleeding (>75 year of age, < 60kg body weight or with concomitant medicines that might increase the risk of bleeding) when the benefits were deemed to outweigh the risk of serious bleeding. Readers were informed that when the efficacy benefits were compared with the risk of serious bleeding events, for every 1,000 patients treated with prasugrel instead of clopidogrel, there were six more major bleeding events but 23 fewer heart attacks. The Panel noted that the press release referred to serious and major bleeding events and that prasugrel had an increased risk of bleeding compared with clopidogrel. In that regard the Panel did not consider that the comparison with clopidogrel was misleading as alleged. No breach of the Code was ruled.

The Panel considered it was very important that press releases, particularly those made available to consumer journalists, were fair, factual and not misleading. Although the Panel was concerned about the content of the press release it considered that, on balance, the circumstances did not warrant a ruling of a breach of Clause 2 which was reserved as a sign of particular censure.

An anonymous Lilly employee complained about a consumer press release (ref UKEFF00062/March 2009) issued by Eli Lilly and Company Limited and Daiichi-Sankyo UK Ltd to mark the launch of Efient (prasugrel) in the UK.

COMPLAINT

The complainant stated that he was increasingly frustrated at his company and had reached his limit with this press release. Prasugrel was a good medicine but needed to be used with caution. There could be significant issues with bleeding but these could be minimised by carefully considering the patient. Indeed, it was part of the marketing authorization that a risk minimisation programme was carried out. The consumer press release, made a lot of the deserved superior efficacy of prasugrel over clopidogrel [Plavix, marketed by Sanofi-Aventis]. But then it went further and made a cheap point about 25% resistance when it was well known that this study was from a 60 patient study in primary percutaneous coronary intervention (PCI). The safety section described bleeding as epistaxis, haematuria when actually there were significant higher fatal and life threatening and minor and major bleeds. In an attempt to dislodge clopidogrel from its pedestal, Lilly appeared ready to sacrifice safety, pushing the use of this medicine beyond its PCI indication.

When writing to Lilly, the Authority asked it to respond in relation to Clauses 2, 9.1 22.1 and 22.2 of the Code. Lilly noted that the product was co-promoted with Daiichi-Sankyo in the UK and the two companies submitted a joint response.

RESPONSE

Lilly and Daiichi-Sankyo explained that Efient was indicated to prevent atherothrombotic events, when co-administered with acetylsalicylic acid, in patients with acute coronary syndrome (ACS) (ie unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI]) or ST segment elevation myocardial infarction [STEMI] undergoing primary or delayed PCI.

The grant of the European marketing authorization for Efient required Lilly and Daiichi-Sankyo to provide health professionals with important educational information regarding the safe and effective use of the medicine, as part of a broader risk minimisation programme. This educational information was appropriately incorporated in all Efient promotional materials and the launch consumer press release in question. Aligned to this requirement, this press release, in addition to Lilly/Daiichi-Sankyo's procedure for reviewing and certifying materials, had been pre-vetted and approved by the Medicines and Healthcare products Regulatory Agency (MHRA). This ensured compliance with the regulatory requirement that the following key educational information regarding safety was appropriately represented in Efient materials:

- Severe, including fatal, haemorrhagic events were more frequent in patients ≥ 75 years of age or those weighing < 60kg.
- Treatment was generally not recommended for patients of ≥ 75 years of age.
- If, after a careful individual benefit/risk evaluation by the prescriber, treatment was deemed necessary in the ≥ 75 years of age group then following a loading dose of 60mg, a reduced maintenance dose of 5mg should be prescribed.
- Patients weighing < 60kg should have a reduced maintenance dose of 5mg.
- The evidence for a 5mg dose was based only on pharmacokinetic/dynamic analyses and no clinical data currently existed on the safety of this dose in the at risk sub groups.

Accordingly, there was no basis to support the allegation in the press release. The companies stated that patient care and safety was at the heart of what they did and they rejected the allegation.

Lilly and Daiichi-Sankyo noted that the complainant had stated that the press release made a lot of the superior efficacy of prasugrel over clopidogrel but made a cheap point about 25% resistance when this study was from a 60 patient study in primary PCI. The allegation was factually and contextually misleading. The sentence in the press release to which the complainant referred stated:

> 'However, research has also shown that up to 25% of patients do not respond adequately to clopidogrel.'

This statement in the press release was substantiated by reference to two peer-reviewed publications Matetzky *et al* (2008) and Matetzky *et al* (2004); Matetzky *et al* (2004) related to a 60 patient study as suggested and the other related to a 200 patient study. Matetzky *et al* (2008) included 200 patients with acute myocardial infarction, presenting within 12 hours of symptom onset. The study authors stated – 'Previous studies have shown significant variability in platelet response to clopidogrel therapy in patients with coronary artery disease, with up to 25% of patients classified as nonresponders to a conventional dose of clopidogrel.' Further, there existed a considerable body of published evidence which demonstrated that resistance to clodpidogrel varied amongst patients; a matter of some considerable therapeutic importance. Serabruany *et al* (2005) stated that 'Clopidogrel "non-responsiveness" has been reported to be present in as little as 5% to as many as 56% of patients who are undergoing coronary stenting.'

The relevance of this information was clearly established and presented in the context of the under-use of heart medicines, the longstanding availability of clopidogrel and the National Institute for health and Clinical Excellence (NICE) recommendation of the use of clopidogrel in the treatment of ACS; this was evidenced by the text which preceded the above statement:

> 'Despite current guidelines, heart medications for ACS PCI patients are underused. When anti-platelet drugs are used, the risk of heart attack, stroke or death

> is reduced significantly. The National Institute of [sic] Health and Clinical Excellence (NICE) recommends aspirin with clopidogrel in ACS treatment.'

Leading up to this section, the press release highlighted that Efient offered an alternative therapeutic option in the management of ACS PCI, which to date had centred mainly on the use of clopidogrel. In this regard the discussion of clopidogrel treatment, the issue of resistance to it in some patients and the implication of this for patients was pertinent and reasonable. Indeed in this regard the press release did not raise unfounded hopes for successful treatment as implied by the complainant. This information was presented in a factual and balanced manner and could not be considered to be 'making a cheap point' or to be misleading. Accordingly, the companies rejected the allegation.

The safety profile of Efient was evaluated in the key clopidogrel-controlled study; TRITION TIMI.38. In the latter, patients with ACS undergoing PCI were treated with Efient and showed an increased risk of major and minor bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) classification system. As a result the Committee for Medicinal Products for Human Use (CHMP) recommended that the use of Efient in patients at increased risk of bleeding should only be considered when the benefits in terms of prevention of ischaemic events were deemed to outweigh the risk of serious bleedings.

It was this background that guided the detail and context in which the risk of haemorrhagic events was discussed both in general and with particular regards to certain patient types and the risk/benefit associated with Efient treatment compared with clopidogrel. Lilly and Daiichi-Sankyo categorically refuted the complainant's assertion that they had intentionally misled the audience regarding the haemorrhagic safety profile of Efient. To support the allegation, the complainant had misrepresented the precise wording of the press release which stated the following:

> 'The most common bleeding events seen with prasugrel in clinical trials were haematoma (a collection of blood under the skin or in a muscle), epistaxis (nosebleeds), gastrointestinal haemorrhage (bleeding in the stomach or gut), haematuria (blood in the urine) and bleeding from needle puncture sites.'

These bleeding events were qualified in the press release as being 'the most common' which was consistent with the Efient summary of product characteristics (SPC) (reference to which was provided with the press release).

Given the intended consumer audience, Lilly and Daiichi-Sankyo believed that it was not unreasonable that the press release, in order to give balance, referred to undesirable effects, including haemorrhagic events, and that the commonest of these were named. The companies noted that the discussion of the commonly occurring haemorrhagic events was preceded by the following explicit statement regarding the increased risk of bleeding associated with Efient relative to clopidogrel the current mainstay of ACS PCI treatment:

> 'All antiplatlet drugs come with a risk of bleeding. Treatment with prasugrel had an increased risk of bleeding relative to treatment with clopidogrel.'

This statement also related to the last paragraph on this particular page of the press release where the increased propensity of 'major bleeding events' associated with Efient compared with clopidogrel was referred to. Given the latter, the companies failed to comprehend the complainant's assertion that they had intentionally compromised patient safety by minimising the extent and nature of the haemorrhagic events associated with Efient treatment or the implication that by doing so they gained an unfair advantage over clopidogrel.

On the basis of the above, the companies' view was that the consumer press release was factual, balanced and did not mislead with respect to the safety of Efient. Accordingly the companies rejected the allegation.

With regard to the complainant's assertion that, in an attempt to dislodge clopidogrel from its pedestal, Lilly and Daiichi-Sankyo were ready to sacrifice safety, pushing the use of this medicine beyond its PCI indication, the companies repeated their statement with respect to the previous allegation.

The companies noted that the Efient indication was stated explicitly and without ambiguity within the press release. There was no direct or indirect discussion of any unlicensed indication(s) of Efient as asserted by the complainant. The companies therefore rejected any suggestion that the press release misled with respect to the efficacy and safety of Efient in comparison with clopidogrel, or at all.

The companies also categorically refuted any suggestion that the press release advertised Efient directly to the public or would encourage members of the public to ask their health professional to prescribe Efient, a prescription only medicine, in preference to clopidogrel.

In conclusion, Lilly and Daiichi-Sankyo were cogniscent of their responsibilities with respect to the Code and had ensured that all Efient press materials were consistent with this (including, without limitation, Clause 2, 9.1, 22.1, and 22.2) and of the highest standard and quality.

In response to a request for further information Lilly

and Daiichi-Sankyo explained that activated platelets played a central role in the pathogenesis of atherothrombosis and in the formation of thrombi following coronary angioplasty, with and without stent implantation. Although platelets were activated by a variety of endogenous agonists, adenosine diphosate (ADP) played a key role in initiating platelet aggregation. Efient and clopidogrel inhibited ADP-induced platelet aggregation and, in combination with aspirin, helped improve clinical outcomes inpatients with ACS and those undergoing PCI, in both the acute and chronic phases of treatment.

Several potential limitations of clopidogrel therapy had been reported including its variable anti-platelet effect. Studies had demonstrated that even with higher doses, clopidogrel response variability (ie poor response or no response to treatment) was associated with a significant risk of thrombotic complications following PCI. This topic was discussed by the British Cardiovascular Intervention Society in January 2009. It was evident that the subject of the variability of response to clopidogrel in patients and the putative mechanisms for this were widely reported and a matter of considerable therapeutic importance, particularly given the increased risk of recurrent cardiovascular events in patients with ACS-PCI.

Whilst the body of evidence clearly supported the variability of response to clopidogrel in patients, as measured by platelet inhibition/aggregation, it was also apparent that the percentage variability reported varied widely. This was primarily because there was as yet no agreed threshold of platelet inhibition below which a patient would be considered a non-responder to treatment or standardised methodology employed to detect platelet inhibition. Given the latter, the press release cited a relatively conservative estimate with regard to the inter-individual variability in response to clopidogrel treatment; this helped to ensure a fair and balanced approach to representing the variable response of clopidogrel. Lilly and Daiichi-Sankyo considered that the balance of evidence supported the statement '… research has also shown that up to 25% of patients do not respond adequately to clopidogrel'.

The companies noted that whilst the data often measured non-response to clopidogrel treatment, the wording of the press release did not actually assert that clopidogrel did not work at all; in fact the statement 'The National Institute of [sic] Health and Clinical Excellence (NICE) recommends aspirin with clopidogrel in ACS treatment' helped avoid any such misinterpretation.

PANEL RULING

The Panel noted that the consumer press release marked the launch of Efient in the UK. The press release briefly described the indications for Efient and the efficacy data which had led to the approval of the medicine by the regulatory authorities. Some background information was given as to the prevalence of ACS and the economic impact of heart disease. The press release was not an advertisement per se for Efient and so in that regard the Panel ruled no breach of Clause 22.1.

Readers were informed that despite current guidelines, and evidence of efficacy, therapy was underused. NICE had recommended that patients with ACS be treated with aspirin and clopidogrel. It was noted, however, that up to 25% of patients did not respond adequately to clopidogrel. Although the latter statement was referenced to Matetzky *et al* (2008) and Matetzky *et al* (2004) it was the 2004 study which demonstrated that upto 25% patients with ST segment-elevation myocardial infarction (STEMI) were resistant to clopidogrel. The authors noted that the study was an observational one with a relatively small sample size (n=60) and so it did not allow for definitive conclusions. Nevertheless, clopidogrel resistance occurred in a significant percentage of STEMI patients and was associated with a higher risk of recurrent cardiovascular events. Matezky *et al* (2008) examined the effectiveness of reloading to overcome clopidogrel resistance in patients with acute myocardial infarction reporting in the introduction that upto 25% of patients were classified as non-responders to a conventional dose; ten studies were cited in support of this statement including Matetzky *et al* (2004) which the Panel presumed substantiated the higher incidence of 25%. Serebruany *et al* reported that clopidogrel non-responsiveness had been reported in as little as 5% and as many as 56% of patients undergoing coronary stenting. It was unclear from the published paper which of the cited studies supported the higher incidence.

The Panel noted that in response to a request for further information, Lilly and Daiichi-Sankyo had submitted that although it was clear that there was a variability of response to clopidogrel, the percentage variability varied widely because there was no agreed threshold of platelet inhibition below which a patient would be considered a non-responder and no one standardized method by which to measure platelet inhibition. The companies had cited what they considered to be a relatively conservative estimate with regard to the percentage of patients who were non-responders ie 25%. O'Donoghue and Wivott (2006) reported that between 4% and 34% of patients had been deemed to respond inadequately to clopidogrel depending on the method of testing and the definition of 'resistance' or 'hyporesponsiveness' used. The authors stated that there was confusion about the true prevalence of resistance/hypo-responsiveness and no clear consensus on the definition of clopidogrel resistance. The Panel noted that where a clinical or scientific issue existed which had not been resolved in favour of one generally accepted viewpoint, the Code required special care to be taken to ensure that the issue was treated in a balanced manner (the supplementary information to Clause 7.2 referred). The Panel considered that the statement in the press release 'research has also

shown that up to 25% of patients do not respond adequately to clopidogrel' did not adequately reflect the situation and in that regard was misleading; a breach of Clause 22.2 was ruled. High standards had not been maintained. The Panel ruled a breach of Clause 9.1.

In a section of the press release headed 'Method of action' it was stated that all antiplatelet medicines came with a risk of bleeding and that treatment with prasugrel had an increased risk of bleeding compared with clopidogrel. The common bleeding events were described. It was also stated that treatment should only be prescribed to patients at increased risk of bleeding (>75 year of age, < 60kg body weight or with concomitant medicines that might increase the risk of bleeding) when the benefits were deemed to outweigh the risk of serious bleeding. Readers were informed that when the efficacy benefits were compared with the risk of serious bleeding events, for every 1,000 patients treated with prasugrel instead of clopidogrel, there were six more major bleeding events but 23 fewer heart attacks. The Panel noted that the press release referred to serious and major bleeding events and that prasugrel had an increased risk of bleeding compared with clopidogrel. In that regard the Panel did not consider that the comparison with clopidogrel was misleading as alleged. No breach of Clause 22.2 was ruled.

With regard to the alleged breach of Clause 2 the Panel considered it was very important that press releases, particularly those that were made available to consumer journalists, were fair, factual and not misleading. Clause 2 was used as a sign of particular censure and reserved for such use. Although the Panel was concerned about the content of the press release it considered that, on balance, the circumstances did not warrant a ruling of a breach of Clause 2.

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